

Clouds of Smoke, Confusion and Oblivion

THE Committee of the Royal College of Physicians under Lord Rosenheim which has produced the latest report on the medical dangers of smoking tobacco (*Smoking and Health Now*, Pitman Publishing Company, 10s) is entirely within its rights to complain that the British government has responded inadequately to the first report on smoking which the college produced in 1962. In retrospect, the original report seems to have been more influential abroad than in the United Kingdom. To be sure, the government of the day endorsed the college's conclusion, and there is now also a ban on cigarette advertising on television. But none of the steps which have been taken have significantly decreased the consumption of tobacco and the inexorable increase of mortality from diseases such as lung cancer.

Since 1962 the average consumption of tobacco by adults in Britain has declined a little, from just under 11 lb per head per year to just 9 lb per head per year, but women have continued to increase their consumption of cigarettes, and, thanks to the filter tip, the average consumption of cigarettes by men has remained substantially constant. In their middle years, 70 per cent of men in Britain smoke some form of tobacco. Statistically, women seem hardly to have changed their habits in the past decade, and more than 50 per cent of those between 20 and 40 appear to be smokers. Given the now well-founded association between smoking and various diseases, it is no wonder that mortality rates continue to increase among smokers. The committee of the college of physicians has had the courage to calculate that if present patterns of smoking continue, the annual death rate from lung cancer will increase from about 15,000 to more than 45,000 in the steady state that will be attained in the 1980s; more than ten times what the annual death rate from lung cancer would be if people did not smoke at all.

The awesome consequences of smoking tobacco are by now so plain that the outstanding question is simply that of telling how most effectively to prevent the habit. Understandably, perhaps, because the physicians' committee is medical and neither legal nor polemical in its constitution, the weakest part of the report is that which recommends action to be taken by those wishing to prevent the smoking of cigarettes. The committee asks that doctors should set a better example, that the government should persuade broadcasters and newspapers to help with publicity and that schools (and especially teachers) should play a more vigorous part in dissuading children from smoking. Legally, the committee would like to see cigarette vending machines removed from public places, the prohibition of advertisements and brand promotional devices, tighter restrictions on public smoking, restrictions on smoking at work and in university lectures, warning notices on cigarette packets, more clinics, restrictions on tar and nicotine content and a permanent government committee to coordinate the campaign against tobacco. One interesting and, it might have seemed, unnecessary recommendation is that insurance companies should weight their premiums

against the smoker. All of these suggestions are of course sensible and practicable. The question that remains unanswered is why British governments, Labour and Conservative alike, are slow to act.

The first thing to be said is that there is a strange contrast between the government's unwillingness to act on tobacco and its vigilance in the war of attrition against marijuana. Little is heard of schemes for using police dogs to sniff out tobacco or of urine tests for picking up the metabolites of nicotine. Although there are regulations that prevent the sale of tobacco to children under 15, little is heard of gaol sentences for those tobaccoconists who break the law. Why should British governments be fierce about marijuana and lenient about tobacco? The Royal College of Physicians has a great deal to say about the importance of the tobacco tax, the source of something like 10 per cent of the annual budget, but it is unlikely that sheer financial greed can account for the strange unwillingness to act. A more likely explanation is that it must necessarily be hard for politicians to make effective regulations for limiting a habit to which they are themselves as much addicted as any other section of the population. The chief difference between tobacco smoking and marijuana smoking is that the first is an ingrained and even respectable habit. For the time being, and with luck forever, the second is not.

In circumstances like these there are bound to be serious limitations to the efficacy with which the British government can move against tobacco. It is, however, entirely sensible that there should be a still further increase in the tobacco tax. From the Exchequer's point of view, nothing would be lost if a three-fold increase in the rate of tax were accompanied by a 50 per cent reduction of the smoking habit, but the hospitals and the mortuaries would then be under much less pressure. It would be entirely sensible to insist that all tobacco products, cigars as well as cigarettes, should include in Britain a warning similar to the tougher form of words about the potential dangers to health now about to be introduced in the United States. A more extensive ban on advertising would be desirable, although there can be no certainty that such a scheme would dissuade people from smoking, and there are obvious difficulties in distinguishing between advertising in newspapers and advertising of the kind which street corner tobaccoconists put in their windows.

Frankly, the most effective course would be to make tobacco hard to come by, which is why the suggestion that vending machines should be removed from public places has much to be said for it. And might it not also help enormously if there were tougher regulations than at present to inhibit the sale of cigarettes? One possibility would be to charge much more for a licence to sell tobacco. Undoubtedly it would be hard for a Conservative government to make such an attack on the livelihoods of small shopkeepers, but the importance of the cause may make practicable even this assault on the sentimental belief that Britain is a nation of shopkeepers. It would of course be better still to arrange that cigarettes



could be bought only at establishments set up specifically for that purpose in much the way in which alcohol is sold in a great many states of the USA and in India. In the modern world, with foreign travel being what it is, an attempt to banish tobacco altogether would evidently be futile, but it would be entirely right to arrange that the purchase of tobacco should be difficult, expensive and demeaning.

Short of this ideal, there is plainly much to be done by a willing government to ensure that cigarette smoking is no longer easily condoned, especially among children. There may be very little evidence that tobacco advertising increases the amount of tobacco consumed, but in Britain there is hardly any advertising to suggest that smoking may be bad for people. The British government has so far helped to sponsor three one minute films for showing on television, and the total expenditure for the Health Education Council on work like this amounts to roughly £100,000 a year, less than 10 per cent of what is spent on similar campaigns about road safety. At a time when apparently inexhaustible sums of money are being spent on the advertisement of the characteristics of decimal coinage that ought never to have been devised, surely it is not too much to ask that the government should spend generously in explaining that cigarettes cause lung cancer. At the same time, it would be sensible if medical people were required by their profession to

draw the attention of patients to the proven relationship between smoking and various kinds of diseases, from bronchitis to lung cancer to emphysema. It would also be seemly if television studios made it improper to smoke on camera and if other public figures could be persuaded to do without public exhibitions of their oral dependency.

The parallel between tobacco and drugs such as marijuana is from this point of view more real than politicians are willing to admit. At present, one of the strongest arguments against the imposition of draconian penalties on cigarette smokers is that such measures would bring the law into disrepute. There might, for example, be something to be said for making illegal tobacco smoking in the presence of children, but the habit is so strongly formed that adults would break the law and take the necessarily arbitrary rap that followed. The difficulty, of course, is that there is at present a danger that the truly draconian penalties applied to those caught with marijuana in their possession may rapidly create the same indifference to the law. To be sure, it does not follow from this that marijuana should be made easily available. There is, however, a case for asking that in everybody's interests, in seeking to restrict the use of drugs like this, the public health authorities should rely on campaigns of public education just as much as on the law. If it seems inconsistent to assume that the law is widely disregarded, that is merely one of the complications of life in a modern society.

Not Saying is Not Believing

THE annual report of the Agricultural Research Council for 1969-70 (HMSO, 13s) is a striking but all too familiar example of the public documents intended to create the illusion of an account of a year's work without saying what strategies have determined policy in that period. In 1967, the Agricultural Research Council startled its readers with a detailed argument to demonstrate, at least to its own satisfaction, that an annual expenditure now running at more than £15 million was adequately justified by the resulting improvement in agricultural efficiency. This year, the report is by contrast innocent of this link between means and objectives. The section on administration and finance turns out to contain only a list of those included in the various honours lists last year, a list of degrees and other honours awarded to members of the council's staff, a list of new buildings and a simple balance sheet showing how the money has been spent.

Nowhere does the council explain why research grants to universities have actually declined marginally in a year when general expenditure has increased by 13 per cent, or why studentships have fallen from £17,000 in 1968 to £5,000 in 1969-70. Undoubtedly the council is finding itself carried along by that rational tendency to make the Science Research Council the chief source of student support at British universities, but it would have been sensible as well as courteous—publicly responsive is the current jargon—to have said just why this policy is sensible. And in spite of a good deal of criticism in the past few years of the council's policy of spending most of its money on research institutes of its own or on others

(such as the Rothamsted Experimental Station) with which it is traditionally associated, the latest annual report has nothing to say either in mitigation or defence. The nearest thing to a statement of policy in the annual report is an argument to support the decision early in 1970 that the plant breeding stations supported by the council were within their rights in making some money out of successful varieties put on the market. Certainly there is no hint of the arguments now widely to be heard that research councils such as the Agricultural Research Council, geared as they must necessarily be to practical benefits in agriculture, would be better placed within the Ministry of Agriculture than in the no-man's-land of Haldane economy which they at present occupy.

The pity in all this is that, for all that readers of the annual report may know, the council's case may well be powerful. Large though the council's budget may be in comparison with the budgets of other similar institutions, for example, it is only a small fraction of the £300 million a year which, until now, British governments have paid out to agriculture as food subsidies. And nobody will deny that there may be profit in creative tension between organizations such as the plant breeding stations and the rest of the agricultural industry. As things are, however, and at least so far as the annual report goes, the weight to be attached to considerations like these will not be defined by at least one of the bodies principally concerned. Those with faith in the networks of government committees which eventually determine policy will hold that nothing will be lost if the argument is settled behind closed doors; others, with less faith in the wisdom of the civil service

and its ways, will be less sanguine; but in any case the most serious loss in the trappist course which the Agricultural Research Council has chosen is that an important episode

in the development of public policy on research in Britain will be settled in such a way that nothing will be learned from it.

Where Next with Coal?

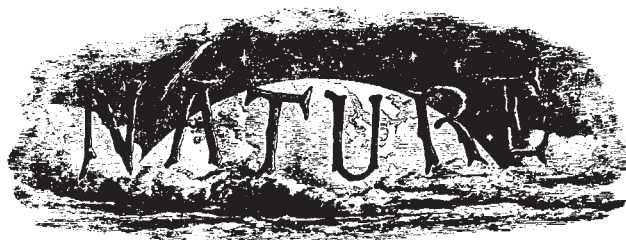
It seems that the British government has set its mind on the replacement of Lord Robens as chairman of the National Coal Board. His term runs out at the end of January and for several months it has been an awkward truth that his successor had not been named, and now he has announced that he will not carry on (as, without question, he would have liked). It is true that it may take the government several months to find somebody to succeed him, but the chances are that before the end of the year he will have paid the price of having interpreted too literally the doctrine that nationalized industries are autonomous organizations that function best when they imitate as closely as possible the methods and the objectives of commercial industry. In the past few weeks, Lord Robens has been protesting that he would not willingly part with those parts of the National Coal Board's empire that consist of hotels, chemical industries and enterprises for exploration for gas and petroleum in the North Sea. Undoubtedly, this impending conflict between the new government and the old chairman of the coal board has been a reminder to many people that Lord Robens can be an awkward customer. As it happens, however, he has also done a good job at the National Coal Board (which is more than can be said of Lord Hall, until recently the chairman of the Post Office Corporation).

It is therefore of some value to recite those parts of Lord Robens's public posture which may be lost when he finally departs. First, he has been a constant critic of the way in which decisions on new capital equipment have recently been made by the Central Electricity Generating Board. Some days before Christmas he was complaining of the folly of having based much of the capital investment programme on large steam turbines none of which had been tested when the orders were first placed. Those chickens have indeed come home to roost, for the CEGB now finds itself without a large part of its theoretically installed generating capacity, while the manufacturers of heavy electrical equipment in Britain find themselves less able to sell plant abroad than they might reasonably expect to be. Much the same has been true of the nuclear power programme. The leaps ahead from one drawing board to another have been too big for safety, with the result that a great deal of money is now tied up in equipment that does not function properly. To be sure, much of the difficulty has been that the British nuclear power industry had not been able to support careful research and development on the proceeds of a flourishing market for nuclear reactors as in the United States, but that of course should have been an argument for caution, not for the rapid evolution of design. Lord Robens does deserve the credit for having made this case at an early stage, but its effect could well have been more noticeable if he had been able somehow to make it more persuasively.

Another of his arguments in recent years has been that fuel policy in Britain should be determined neither by the

government (which means the civil service) nor by the nationalized industries for coal, electricity and gas acting independently of each other, but by a fuel commission organized in such a way as to give advice to governments which can only be rejected at great risk. Shorn of some of the exaggerated and naive trappings of government by rational and like-minded oligarchs to which Lord Robens lent his name some years ago, this is a sensible idea that deserves to be examined seriously. For the difficulty in deciding what fuel policies to pursue is that governments are necessarily preoccupied with much more immediate considerations than can be appropriate within the industry. The time taken to build a nuclear power station is, after all, far longer than the constitutional duration of a single British parliament. Some of the alarming consequences of this have been apparent in the way in which British governments have intervened in decisions about the kinds of fuel to be used in particular power stations when they have feared trouble from interested parties, usually local colliers. A fuel commission could prevent a great deal of trouble of this kind but, more positively, it could create the kind of framework within which much more accurate account could be taken than at present of some of the important but indirect costs of the development of all fuel industry—such things as the cost of capital, the cost of providing an assured supply come cold or warm and the cost of keeping the environment decent. Even when Lord Robens goes, there is everything to be said for giving his fuel commission a chance to prove itself.

100 Years Ago



NOTES

OWING to Mr. Lockyer having been summoned to Malta to give evidence at the court-martial on the commander of the unfortunate *Psyche* (which we regret to hear has not been saved), we are unable to give a detailed report of the proceedings of the Sicilian Eclipse Expedition. We understand that Mr. Brothers, who was stationed at Syracuse, obtained five photographs of the Eclipse during totality. One of these shows the corona "as it was never seen on glass before." At Augusta very little was seen; but at Syracuse, the southernmost station of all, the clouds which concealed the earlier stages of the Eclipse, passed away from the sun about five minutes before totality, "disclosing," writes Mr. Brothers, "a scene I shall never forget." Next week we shall hope to be able to give a complete account of the results of the Expedition, and their bearings on any increase of our knowledge of Solar Physics.

From *Nature*, 3, 212, January 12, 1871

OLD WORLD

CHEMISTRY

Poor School Image

A CRITICAL examination of the state of chemistry teaching in schools, and of career prospects in chemistry and allied subjects, took place at a conference sponsored jointly by the Royal Institute of Chemistry and the Institution of Chemical Engineers at Imperial College, London, this week.

The scope of the conference, entitled "Chemistry for the 70s", complemented and slightly overlapped the terms of reference of the Eaborn committee which was set up to study the relationship between university chemistry courses and the needs of industry (Royal Institute of Chemistry, £2). The Eaborn committee report highlighted the poor quality of the applicants for university chemistry courses, and told a story of poor job prospects for qualified chemists. But it failed to come properly to grips with the problems involved (*Nature*, 228, 1242; 1970).

The morning session was chaired by the President of the Royal Institute of Chemistry, Professor Sir Ewart Jones, and was devoted entirely to the problems of teaching chemistry in schools. Lord Wynne-Jones, formerly professor of chemistry at the University of Newcastle, spoke of the need for the more enlightened teaching of chemistry as an integral part of a balanced education of all children, regardless of their future careers. If the idea of chemistry as a discipline could be put in its proper place and the hours of traditional laboratory work reduced and revitalized, the excitement of chemistry and its relevance to everyday life could be emphasized properly. Topics such as pollution, he said, should be talked about in their scientific context in schools, and interest in chemistry as a subject would follow naturally for many children.

During the remainder of the session four speakers, two of them schoolteachers, outlined the practical difficulties of teaching chemistry as part of a general liberal education in secondary schools, and suggested some of the possible solutions. The general picture, as in the other physical sciences, is one of a shortage of scientifically qualified teachers, but a shortage which is by no means as critical as in physics and mathematics. The trouble seems to be that only a small proportion of teachers have been much exposed to science during their own education or training, and the ability to inculcate the right sort of reasoning in children by asking the right questions is often conspicuously lacking. A clue to the possible reasons for the lack of college-trained chemistry teachers, for example, may lie in the figures given in the Eaborn report which suggest that

university chemistry departments are accepting applicants with the lowest grades of A-level pass, leaving the colleges high and dry. During the discussion which followed, a representative of the National Union of Teachers laid the blame for the whole situation squarely at the door of the tripartite system of higher education and called for the introduction of a comprehensive university system to incorporate universities, polytechnics and colleges of education.

Both Mr M. P. Berry, a grammar school teacher, and Dr M. A. Jensen, who teaches in a large comprehensive school, took pains to emphasize the need for good teaching of first to third year secondary schoolchildren by scientifically qualified teachers. A few years ago, as many as 40 per cent of these schoolchildren in their first year were taught by non-scientists, and the proportion remained as high as 20 per cent for third year children. They also bemoaned the lack of money made available by local education authorities which on average amounts to only about 0.55p per pupil per period for chemicals, small apparatus and textbooks. Unfortunately local education authorities were not directly represented at the conference, and indeed the only people putting forward the point of view of headmasters were Mr B. C. Harvey and Mr B. J. Moody of the Headmasters' Association.

A number of voices echoed the belief of the Eaborn committee that compulsory training for all teachers was "unfortunate", but they were quickly silenced by Mr M. G. Brown of the University of Sussex who very lucidly pointed out that the quickest way to demoralize any teacher was to require him to teach Nuffield-style chemistry to the lower streams of a comprehensive school without any pretraining.

During the afternoon session, a number of industrialists spelt out their solutions to the problem of the unemployment of graduate chemists, who seem to find it more difficult than other scientists to find suitable jobs. Most of the speakers pointed out that graduate chemists should not find any more difficulty in obtaining employment than arts graduates who usually have to branch out from their field of specialization as a matter of course. Although ICI, represented at the conference by Dr D. S. Davies, and smaller firms such as the Borden Chemical Company, are evidently in favour of chemists and chemical engineers spreading their wings early and entering industrial functions which are not primarily scientific in character, it seems that the majority of industrial concerns only pay lip service to this concept. Several of the speakers suggested that graduate chemists often underestimate their general abilities and this may also be a partial explanation for the alarming pool of jobless chemists at the present time.

At the end of the conference, Professor J. F. Richardson of University College, Swansea, summed up by saying that the nub of the problem seemed to be that children in the age group thirteen to fifteen only received poor background instruction in chemistry and that they could not make a properly considered decision about their field of specialization. He also reiterated the view of many of the participants that the popular image of a chemist was inaccurate and misleading and announced that the Royal Institute of Chemistry and the Institution of Chemical Engineers have produced a booklet—with the same title as that of the conference—which had been circulated to schools in an attempt to set the record straight. The conference agreed to set up a working party, consisting of teachers and their organizations, local education authorities and youth employment advisers, to make recommendations for the improvement of the general status of chemistry and its teaching in schools.

ENGINEERING

NEL wants Sponsors

THE National Engineering Laboratory has had an eventful year. Its future has been in the balance since January last year, when the Green Paper on Government Research, published by Mr Anthony Wedgwood Benn, saw the establishment as part of the proposed British Research and Development Corporation. With the reorganization of government departments which was instituted soon after the Conservative government took office, responsibility for the NEL was transferred from the defunct Ministry of Technology to the Department of Trade and Industry, and in April 1970, Mr R. H. Weir was appointed director of the establishment to fill the post left vacant by the departure of the previous director in October 1969.

But the second progress report of the National Engineering Laboratory—a free, glossy handout extolling the services which the NEL has on offer to industry—records few of the actual and possible upheavals in the laboratory during the period from April 1968 to March 1970. In fact, the report is remarkably similar to the previous progress report.

The NEL's chief problem is to make its services more widely known to industry, and to this end, the progress report records the activities of the laboratory which are likely to appeal to would-be sponsors. Computer aided design, research on the strength and design of components, fluid mechanics, heat exchangers and numerically controlled production all play leading parts in the report.

How successful has the laboratory been during the past years in attracting industrialists to use its facilities? In the

year ending March 31, 1969, the laboratory spent £2,473,100, and received £176,000 from sponsoring firms. Although that record does not seem too impressive, Mr Weir, the new director, points out that it is impossible to set out the financial benefits resulting from the sponsored research against the laboratory's expenditure. "In many cases, firms are unable to measure these benefits and others are justifiably reluctant to have publicized this information which would be useful to competitors", he says. Mr Weir also points out that much of the NEL's work has environmental benefits, such as the development of quieter machines, and the testing of components and gas cylinders.

These hidden benefits notwithstanding, the NEL is looking for more industrial sponsorship and, tucked away in East Kilbride in Scotland, it faces a rather uphill task in getting its name at least as well known as that of the National Physical Laboratory. One answer suggested by Mr Weir is that a full appreciation of the work of the establishment can only be obtained by a personal visit to the NEL.

One of the laboratory's more widely-publicized activities is that of computer aided design. In 1967, a regional experiment was started which allows participants a controlled amount of time on the NEL computer. This experiment is now nearing completion, and one company, Thermotank Products, in collaboration with the NEL and Glasgow University, has found that the cost of its design programme has been reduced by a factor of between 15 and 30 with the use of a computer.

As far as strength and design of components are concerned, the laboratory has been engaged on research into the stress on a variety of materials and components, from ropes to crane jibs. A versatile loading frame has been built for testing large components, and the report points out that the laboratory has a large number of testing facilities available to industry.

PROTEIN

Food from Oil

WITH the annual world protein shortfall now running at between 20 and 30 million tons, the announcement last week that the British Petroleum (BP) hydrocarbon fermentation plant at Grangemouth will be in full production within weeks is welcome news. In this process, microorganisms—yeasts in the BP process—are grown on crude petroleum and the microbial protein is recovered and used as an ingredient in animal foodstuffs.

It has been calculated that the present annual world production of petroleum is sufficient to manufacture 20 million tons of protein, but BP's involvement will be

on a more modest scale. Four thousand tons of 'Toprina', the trade-name BP has given to the protein derived from its process, will be manufactured each year at Grangemouth; and a second plant, at Laverna near Marseilles in France, is scheduled to start production later this year and will have an initial annual capacity of 16,000 tons.

The start of commercial production of protein from petroleum is something of a *tour-de-force* for BP; the protein which will be manufactured in Scotland and France has already been subjected to more than six years of rigorous testing. Although prospects for the manufacture of protein from petroleum for human consumption look bright, the immediate intention is to manufacture only feed for animals. Protein made in BP's pilot plants has been fed successfully to many generations of chickens, poultry and pigs. 'Toprina' is mixed with other ingredients to yield a high protein diet which is of higher nutritional value than fishmeal—a common animal feed—and cost, around £100 per ton, is comparable.

The sustained effort which BP has made during the past few years has certainly paid off, for the company seems to have established a clear lead in this field of food technology—in the West at least. The Chinese are reported to have had a protein plant in operation for some time, and the Russians have been experimenting with paraffin fermentation, but so far no details are available. On the other hand, the 'Toprina' process has stimulated over 200 enquiries from 42 different countries, and a 1,000 ton per year plant has been built under licence in Japan and is already producing protein.

The science behind the process is very simple, but the technology, especially for large scale production, is complicated. BP is at present experimenting with two separate systems. In Grangemouth, the microorganisms are fed with a fairly pure mixture of paraffins, prepared from crude oil by molecular sieving. The microorganisms are capable of assimilating all this hydrocarbon and there is little waste. In Laverna, the microorganisms are raised on gas-oil, a fraction resembling diesel fuel. The yeasts can assimilate only the waxy part of this fraction leaving a much cleaner petroleum fraction. The protein manufactured is thus biological in origin and in nature, and the process is in no sense a chemical synthesis of protein.

There can be no doubt that there is a steadily growing demand for this type of feed product, and the entire production from the BP plant during its first year of operation has already been taken up by leading feed compounders. Nevertheless, in spite of this visible evidence of the commercial viability of the product, BP is shy of divulging its future production plans. The company admits to looking at designs, schemes and locations

for larger plants having the capacity to produce perhaps 100,000 tons of protein a year, but denies that any major decisions have yet been taken.

INDUSTRIAL RELATIONS

Vital Amendment

THE scope of the Industrial Relations Bill is to be extended to include professional organizations such as the British Medical Association and the Institution of Professional Civil Servants. The government has given an undertaking that the bill will be amended during the committee stage, and it seems likely that a register of professional organizations will be set up under the auspices of the proposed Registrar of Trade Unions.

If the bill is passed and implemented in its present form, professional organizations would be placed in an anomalous position. Under the terms of the bill, they would be regarded as organizations of workers, but would not be guaranteed the same rights and protection as registered trade unions. A professional organization which advises its members to take industrial action, for example, would be liable to heavy fines, while a registered trade union would be protected against actions for damages if its members break personal contracts with the union's sanction. The bill does, however, include provision for court actions to be brought against a trade union which breaks a contract which it has itself negotiated.

The British Medical Association and the British Dental Association are likely to be most affected by such an amendment to the Industrial Relations Bill. For one thing, their members hold personal contracts with the National Health Service, and both associations would, under the terms of the bill, have been liable to court actions when they advised their members to break contracts during the salary negotiations last year. With their hands tied in this way, professional organizations would lose members to registered trade unions, such as the Association of Scientific, Technical and Managerial Staffs, because such unions would be able to set themselves up as the only organizations capable of negotiating effectively on salaries and conditions of employment. The Association of Scientific, Technical and Managerial Staffs has already absorbed the Medical Practitioners Union.

Engineering associations will be less affected because they formed the United Kingdom Association of Professional Engineers, to negotiate conditions of employment. Similarly, the Association of University Teachers was affiliated last year to the Trades Union Congress, and the machinery used recently to negotiate salary scales for university academic staff would be approved under the terms of the bill.

ANTARCTIC ICE

Traces of Dust

SAMPLES of ice collected from an area near the British Antarctic Survey Base in Halley Bay are being brought back for study in Britain. The study, carried out by a team from the University of Bristol, will help in the investigation of how pollutants spread around the Earth, and might eventually produce traces of extra-terrestrial dust. As a rehearsal for the project, foot cubes of snow were collected by members of earlier expeditions stationed in Halley Bay but, for the first time, a geochemist, Mr David Peel, has visited the region for the express purpose of gathering snow and ice samples for analysis at his home laboratory.

The samples collected in the rehearsal were packed into tin boxes and kept under refrigeration until they could be studied in dust free conditions at Bath University. A preliminary analysis by Dr D. Parkin and his colleagues involved trimming the ice blocks with a hot wire knife before allowing the uncontaminated interiors to melt in clean containers. A mere 0.1 µg of wind-borne dust was found in an initial mass of 70 kg of ice. No particles greater than one micron in diameter were found, and this very small amount of possible wind blown dust suggests that efforts being made by Professor E. Picciotto of Brussels University to detect extraterrestrial dust in polar ice samples, may not go unrewarded.

For the more detailed study now planned, about a thousand kilogrammes of ice will be taken from sites along a path inland from Halley Bay. At Bristol, some of this sample will be studied for evidence of organic debris and pollutants such as DDT and lead. Because the samples are taken in the form of slabs at different levels down the walls of trenches dug in the ice, some indication of the change in pollutant content over the years should emerge from the study. Mr Peel

is also carrying out on-the-spot analysis with a gas chromatograph, and some of the laboratory work will again be carried out by Dr Parkin's group in Bath.

The expedition is under the overall supervision of the Scott Polar Research Institute in Cambridge. As the onset of the Antarctic winter makes the Halley Bay region inaccessible to ships after February, Mr Peel and his samples will shortly be leaving the Antarctic, and should be back in Britain by April or May.

RUSSIA

Collective Science

from our Soviet Correspondent

FOLLOWING the adoption of the new Five Year Plan and the new state budget by the Supreme Soviet (see *Nature*, 228, 1130; 1970), concrete measures to implement the plan are now being announced. Particularly emphasized is the position of the Soviet Union in the "scientific and technological competition with the capitalist world" (*Pravda*, 29 December, 1970) and, accordingly, many of the measures announced are of a practical and technical nature, such as the proposed introduction of more than 600 new types of "machines, instruments, equipment and materials" in 1971.

Some more general measures are also foreseen. The organization of "collectives" of scientists to deal with individual problems of the national economy is to be intensified. These are to be based in particular in Moscow, Leningrad, Ukraine and Byelorussia. The Siberian branch of the Academy of Sciences and the All-Union Academy of Medical Sciences will also play a leading part in the work of these collectives. One of the largest such groups already in existence is that of the Donbass, in which scientists from no less than 76 institutes and technical colleges take part.

Although the percentage expenditure

on "education, science and culture" in the new budget has decreased from 16.2 to 16 per cent, the absolute expenditure on higher education is to be slightly greater in 1971. A number of new institutes and colleges are planned, chiefly in Ukraine, and in the expanding areas of Siberia and the Urals.

FLOODING

Yorkshire's History

FLOODING of the rivers in Yorkshire is such a relatively common feature that there should be a concerted long term programme in any area of urban renewal to widen the course of the River Wharf or the River Ouse. That is the conclusion reached by Mr J. Radley and Mr C. Simms, joint authors of a historical survey of Yorkshire flooding from the fourteenth century to the present (*Yorkshire Flooding*, William Sessions, 10s). They also believe that there is a good case for establishing a wildfowl refuge in the lower reaches of the rivers Ouse and Derwent, to protect the varieties of wildlife attracted to the flooded areas.

The survey is an interesting account of the way in which urban and agricultural development has affected the pattern of flooding in the Yorkshire rivers. Dredging, straightening and embanking of the natural waterways have helped to canalize floods so that they run off seawards, but one result of flood banking is that the return of flood waters into the rivers by natural means is often an impossibility. The net result of these developments, according to the authors of the survey, is that the variety of the massive floods that were witnessed in the past are no longer experienced, but they warn that there will be an increasing number of major floods as the drainage of catchment areas is perfected.

In the Vale of York, the most densely populated area liable to flooding discussed in the report, the chief culprits are snow melt, aggravated by frozen soil, and, in the summer, violent thunderstorms following a wet period. These factors have resulted in major flooding of the Ouse in 1929, 1932, 1933, and especially 1947, but none of these compare with the great floods witnessed in the fifteenth and sixteenth centuries. In 1625, for example, the River Ouse burst its banks, reached its highest mark ever on the York City wall, and flooded a large area of the vale. Floods in the Vale of York tend to be particularly frequent and unexpected because the flood may come down one or any combination of rivers feeding into the vale. One result of these constant changes in the water table is that the foundations of York Minster have been made very unsafe. In 1968, water entered 150 buildings, including a hotel designed to keep essential services above the flood.

PHYSICS

Heisenberg Retires

from a Correspondent

PROFESSOR WERNER HEISENBERG, at a ceremony in Munich last month, formally relinquished his directorship of the Max-Planck Institute for Physics, after nearly thirty years in office. Addressing members of the Institute, Professor A. Butenandt, President of the Max-Planck Gesellschaft, said that although difficulties in finding a successor to Professor Heisenberg have not been resolved, this does not reflect any indecision about the future role of the Institute for Physics. Overall direction of the scientific programme of the institute will be undertaken temporarily by Professor H. P. Dürr, with Professor L. Biermann in administrative charge of the several subsidiary institutes.

Professor Dürr, said that particle physics will continue to spearhead the Institute's research programme, and he emphasized the need for an even more integrated research effort, with closer experimental-theoretical cooperation in the central institute, furthered by a new "phenomenological group". There will be the fullest possible cooperation with CERN and other outside bodies and the amount of remote data analysis carried out in Munich can be expected to increase.

NEW WORLD

Dissent Blooms at AAAS Circus

by our Washington Correspondent

"SCIENCE is a sacred word to me," Dr Edward Teller proclaimed at last month's meeting in Chicago of the American Association for the Advancement of Science, "but there are those who want to make it into a political circus." Circus is not too inaccurate a description of a meeting that heard little science, sacred or otherwise, but witnessed a succession of theatrical disruptions which chairmen of sessions were mostly unable to control. Dr Teller, father of the American H-bomb, had to share his platform with placards proclaiming him a war criminal; Dr Glenn T. Seaborg, chairman of the Atomic Energy Commission and newly elected president of the AAAS, fled the room rather than hear himself indicted for the crime of "science against the people"; the president of the National Academy of Sciences, Dr Philip Handler, escaped lightly in being called a lackey of the ruling class by a speaker who usurped his podium; and several sessions were disrupted altogether by small groups of hecklers, one of whom was punctured in the arm with a knitting needle wielded by the enraged wife of a professor of biology.

All these antics, which occurred in the dull days between Christmas and the new year, when the AAAS holds its annual meetings, received wide coverage in the press and on television, and must have conveyed graphically to a bemused public that the scientific estate is passing through a troubled period. The other headline catcher of the meeting, the report of a group commissioned by the AAAS a year ago to study the effects of herbicide spraying in Vietnam, confirmed in lower key the theme of disquiet at the military uses of science which was a chief target of the dissenters' protests.

The Secretary of Defense announced a phaseout of herbicide spraying on December 26, just three days before the Herbicide Assessment Commission delivered its report to the AAAS, and insofar as the former event may have been influenced by the latter, Dr Matthew Meselson and his colleagues on the commission have forced a giant organization to change its policy in a victory comparable perhaps with Mr Ralph Nader's triumphs over General Motors.

Besides the protests of the radicals and the report of the herbicide team, the third significant sign of revolt against the established order at the AAAS meeting was an assault on the National Academy of Sciences delivered by a former Secretary of the Interior, Mr Stewart L. Udall. In words more stringent than the blanket

abuse of the radicals, Mr Udall castigated the academy for having served as a virtual puppet instead of as an independent critic of government.

The scientific community is perhaps more responsive to such criticisms and more ready to question the practices of the science establishment in Washington now that the establishment is proving unable to keep the cornucopia flowing. The president of the National Academy outlined some of the reasons for the malaise among his constituency in the first formal address of the AAAS meeting. "The system," Dr Handler confessed, "is in retreat. There has been a 20 to 25 per cent reduction in federal support for science. To what extent the scientific enterprise may be imperilled is unclear. . . . In radio astronomy and particle physics our leadership is being lost to other nations. Many medical schools are on the brink of insolvency. The employment prospects of the 1971 PhD class seem forbidding. The morale of the scientific and academic communities may soon be broken. The scientific enterprise has not been dismantled but there exists a level of apprehension far deeper than the present fiscal problems."

The gloomy outlook of Handler's speech together with the diversions put on by the radical protesters—a rhetorical denunciation of the government's use of science and a leaflet attacking Handler's views on the academy's obligations to do work for the Department of Defense—served as an accurate foretaste of what was to come. The highlight of the next day's session was a symposium entitled "Is there a Generation Gap in Science?", at which two venerable Hungarians, Edward Teller and Albert Szent-Györgyi, represented one side of the age gap and opposite sides of the political spectrum. "I see only one widening gap", the 77 year old Szent-Györgyi said, "the gap between science and society, the gap between the present course and the desire of the great silent majority of making for peace, goodwill and decency. . . . Because science is used for war, we have lost the respect of the people and there is a revulsion against scientists. . . . The bombs dropped on Vietnam make bombs go off in Wisconsin."

Szent-Györgyi judged the mood of his audience better than Teller, who had arranged for the Conrad-Hilton to provide him with five bodyguards, an absurd miscalculation that was a gift to those in the audience seeking to embarrass him.

A member of the radical group, known

as SESPA (Scientists and Engineers for Social and Political Action), raised objection to discussion taking place under the guns of Teller's bodyguard, a procedural point that was stoutly disposed of by Margaret Mead, chairing the discussion. Later, another SESPA member appeared on the platform with the word "Bodyguard" emblazoned across his vest and stood sentinel behind one of the speakers for the remainder of the session. Teller was also obliged to share the platform with two other SESPA members who throughout his speech raised a series of placards proclaiming him a war criminal and bearing quotations from his statements on nuclear war.

With his forceful delivery, thick Hungarian accent, and a fair measure of ham-acting, Dr Teller soon bludgeoned the bulk of the audience to his side, many of whom in any case had been alienated by the protesters' modes of interference. Reminding his listeners he was a Jew who had lived in Nazi Germany, Teller proclaimed that "As now, I was then under attack of thoughtless individuals whose actions were liable to produce violence and lack of reason." "We scientists", Teller declared, "should concentrate on science and not politics. In a democracy it is for the people to decide how the new results of science should be applied. We scientists should bring our own house in order, and bring order to the universities."

Teller was followed by Dr Richard P. Novick of the Public Health Research Institute of New York, who made a strong statement in favour of scientists seeking to influence the ends to which their research is put. "It seems to me that if we as scientific workers were to organize ourselves along classical union lines we could be an effective social force for the public good—could use our knowledge to support demands that the fruits of our research be used to serve society as a whole. . . . By such actions it may still be possible without a bloody revolution to radically reorganize this society so that it serves the people and is therefore unable to misuse our science." At the end of his speech Novick turned to Teller and on behalf of the SESPA group presented him with the second annual Dr Strangelove award "In recognition of his service in the cause of war". The trophy, which Teller declined to accept, is a policeman firing a pistol, with the motto "I am just following orders".

Apart from the false step over the bodyguards, Teller's handling of his opposition was well practised and deft,

allowing him to turn the situation to his own advantage. Dr Glenn T. Seaborg, the only other speaker who faced as strong an opposition, chose to avoid rather than confront his antagonists. The occasion was the final afternoon of a long and on the whole tedious symposium entitled "Science and Federal Government 1970" at which past and present luminaries of the Washington scientific establishment reminisced of warm evenings on Constitution Avenue in 1937, and wondered how to counteract the anti-science attitude among the young. More relevant than these discussions was the advice tendered by Congressmen John W. Davis and Charles A. Mosher (the chairman-to-be and senior Republican member respectively of the house subcommittee on science, research and development), both of whom strongly advised the scientific community (in Mosher's words) to "get over your traditional aloofness from the political process, stop preaching to the converted", and "take your case vigorously and skilfully to the public and to the Congress". Dr Seaborg, the final speaker in this three day symposium, was to have delivered an address that (in its printed version) contained no reference to the three topics in which his audience would surely have been interested—the controversy that surrounded his election as president of the AAAS (see *Nature*, 228, 1023; 1970), the criticism by environmentalists that the Atomic Energy Commission has been both advocate and judge of its own case, and the extent to which scientists should be involved in politics. Seaborg was prevented from not saying any of these things by a determined body of SESPA members, about a dozen in all, who moved to the front of the auditorium as the previous speaker finished and read out through a megaphone an indictment of Seaborg "for the crime of science against the people". The disruption had been anticipated and the room was full to capacity with a swollen audience and the apparatus of several television crews. Before the SESPA spokesman, Herbert Fox of Boston, had begun to read the indictment, Seaborg had slipped out of the room by a side exit. The indictment, like the other SESPA activities, was intended more as a harmless piece of theatre than a factual criticism, and attacked the offices that Seaborg has held rather than Seaborg the man, being devoid of specific or personal detail.

The indictment having been declaimed in the absence of the accused, the megaphone was handed over to several young women members of SESPA who inchoately harangued the dwindling audience on the disadvantages faced by women in science and society. The chairman of the symposium made no attempt to bring the meeting back under his control or to ask the SESPA group to explain their action, and the final session of AAAS

dissolved on a loud, clear note of confusion, with the disrupters having spoken the finale.

The routing of Seaborg by the SESPA group, however, was merely a symbolic victory over the science establishment. In a parallel session a much more serious attack on the same target was being made by a former Secretary of the Interior, Stewart L. Udall. Deriding the conventional practice of the science establishment in rendering technical advice and services to government without regard to their political implications, Udall described this attitude as one that tended "to make scientists political eunuchs—mere technicians detached from a value system and its attendant 'political' judgments. . . ." The former Secretary reserved his fiercest criticism for the National Academy of Sciences which, he said, "by confining itself to a clientele almost exclusively made up of government agencies, and by permitting its clients to phrase the questions that it will study, has all too often become a mere adjunct of established institutions. . . . There are good reasons if some segments of youth are disillusioned with science in the 1970s. While courageous individuals in the scientific community were raising the alarm about the lethal threat of chemical and biological warfare, what was the academy doing? It was working under contract to the Defense Department to select bright young scientists to work in the Defense Department's Chemical and Biological Weapons Centre."

Beside this radical onslaught, much of the argument of those who would call themselves radical looks pale and ineffective. But the influence of the SESPA group on those attending the AAAS was almost certainly more considerable than might be judged from the often self-defeating disruptions of public sessions and the rhetorical, unspecific nature of the group's broadsheets. The late night meetings held to discuss the day's activities and plan the morrow's were regularly attended by up to 200 people, and as the conference wore on, more and more SESPA badges (bearing the motto "Science for the People" beside a red clenched fist and a hand holding a chemical flask) were to be seen in the lobbies of the Conrad-Hilton Hotel. The SESPA group, consisting of about a dozen full time workers, operated out of a room provided free through the AAAS by the hotel. With the aid of a duplicating machine and volunteer labour the group managed to conduct a series of anti-meetings in parallel with the AAAS activities, as befits the non-organization that SESPA claims to be.

SESPA was born at the meeting of the American Physical Society in January 1969, in reaction to the society's voting down of an amendment which would have authorized it to take a stand on the

Vietnam war. SESPA's object is to make clear the political nature of science. Any group of people may call themselves members of SESPA, and it was a group in Boston named Science for the People that first erupted on the AAAS at its annual meeting in Boston last year.

The beliefs of the group, not immediately accessible from its literature, received what was probably their clearest articulation at the AAAS symposium on scientific organizations and the public policy process. According to Brian B. Schwartz, leader of the Theoretical Physics Group at the MIT National Magnet Laboratory and one of the founders of SESPA, "If you practise science without working for change, you are not working for the people—what the radicals are doing is making it clear that science always has and always will be involved in politics. . . . We don't mind about the atomic bomb and the decision to drop it—the thing is, have we developed any institutions to prevent another such situation happening?—No, because we still insist that science and politics are separate."

The chief object of SESPA's activities at the AAAS meeting insofar as it had one (planning was cheerful and disorganized) seemed to be to demonstrate the simple truth (as SESPA members believe) that science is political. The theatrical gestures and noisy disruptions may have got this message across, even if nothing else, to a largely hostile or indifferent audience. The empty rhetoric of the pamphlets attacking Handler, Teller and Seaborg may have served a similar purpose. The effectiveness of these tactics was debated at each night's SESPA planning meeting (which was open to all and regularly attended by members of the AAAS staff and council); for example, the feeling of the audience seemed to be against an extremist suggestion that Teller should not be allowed to speak and there was also criticism of demonstrators who had managed to get their pictures into the "pig press" but no statement of SESPA's position. Some SESPA members felt that AAAS speakers should be listened to before they were interrupted, but another view was that "the purpose of a disruption is not to educate the speaker—he is our enemy. He's not here to educate us—we are here to educate him."

Whatever the political impotence or otherwise of the AAAS, the radicals' criticism of its annual meeting is probably true as far as concerns the quality of science presented. Many scientists prefer to present new results at more prestigious meetings, such as those sponsored by the American Physical Society or the American Chemical Society.

SESPA's bimonthly publication, *Science for the People*, can be obtained from SESPA, Box 59, Arlington Heights, Mass. 02175. Annual subscription \$10.

NEWS AND VIEWS

Watershed in X-ray Astronomy

To a certain extent the article on page 96 of this issue of *Nature* from the X-ray astronomy group at the Massachusetts Institute of Technology is a record of disappointments. That is not to say that the data reported there from rocket flights carried out since 1967 have not been valuable—the work by the MIT group on the untangling of the X-ray sources in the direction of the centre of our galaxy is generally regarded as the best of its kind—but it is clear that the group has not achieved what it has been searching for; the identification with visible objects of the X-ray sources near the galactic centre. Now that the first satellite to be devoted to X-ray astronomy has been launched, and is apparently working successfully, the MIT article and another from the same group which is in next Monday's *Nature Physical Science* are in some ways a record of what has been achieved in specific areas by rocket-borne X-ray detectors (for a summary of the second MIT article see page 84 of this issue).

The way that many X-ray sources are concentrated in the constellations Scorpius and Sagittarius, the direction of the galactic centre, has been a problem almost since the days immediately after the discovery of Sco X-1 in 1962 which started X-ray astronomy. That the sources are contained within our galaxy, and are not scattered through intergalactic space like galaxies and quasars, is certain from the way the sources are concentrated in the direction of the galactic centre, which is why they are given the prefix GX for "galactic X-ray source". It is now known that the concentration of sources is unlikely to be in the Sagittarius spiral arm of the galaxy; extrapolating this density of sources to the other arms would lead to an estimate of the total emission of X-rays from the galaxy exceeding that which is observed.

It is disappointing, however, that the boost given to X-ray astronomy by the identification of Sco X-1 with an anomalous object having large ultraviolet excess has petered out as far as the sources near the galactic centre are concerned. Objects as anomalous as the visible counterpart of Sco X-1 are rare, so it might have seemed good enough to fix the positions of the sources to a few minutes of arc and then scan the error rectangle for peculiar objects. Yet this subjective approach has not so far turned up any likely identifications, even when the positional accuracy has been at its best. In September the MIT group reported positions with error circle radii of between 1.2 and 2.6 minutes of arc for four of the Sagittarius sources, using a system known as a rotating modulation collimator, which compares with previous error circle radii from 10 to 20 minutes. Even so, none of the sources could be identified with anything visible (nor could any radio emission be detected, which seems to rule out supernova remnants); the error circles contain a few tens of objects, none of which seem remarkable

enough to warrant an identification (*Astrophys. J. Lett.*, **161**, L161, 169 and 173; 1970).

What this seems to mean is either that the sources are not anomalous like Sco X-1, at least not at visible wavelengths, so that positions will have to be accurate to a few seconds of arc rather than minutes before there can be successful identifications, or that the sources are too far away to be visible or are blotted out at visible wavelengths by obscuring matter.

In spite of the failure to identify any of the sources the MIT group has done good work by making the direction of the galactic centre less confusing. The positions which are given in this week's article for eleven distinct sources that have been recognized will be the basis for future work. Following the successful launch of the first Small Astronomy Satellite in December, however, which will revolutionize X-ray astronomy by breaking astronomers' dependence on brief rocket and balloon flights, the articles from MIT take on the appearance of a swansong. It is clear that X-ray astronomy will never be the same, at least not in the 2 to 20 keV band covered by the satellite and which has been popular among the groups using rockets. One estimate is that the ability to detect objects thirty times fainter than the present limit which the long observing times of the satellite confers will increase the number of known X-ray sources from about forty to several hundred. For reasons like these, X-ray astronomers using rockets have been looking over their shoulders a lot recently, and many have been moving to lower energies—less than 1 keV—which are so far not covered by satellite experiments. At higher energies than those covered by the new satellite, the large detector sizes and long integration times needed mean that balloons are in many ways preferable to rockets in any case. Even so, the rocket work will still stand—now that it is realized that some X-ray sources vary in strength with time, the rocket measurements of the strength of X-ray sources during the sixties will always be valuable.

Yet the satellite X-ray detector, designed by the group at American Science and Engineering, Cambridge, Massachusetts, does not have a sufficiently good resolution to solve the problems of identification raised by the MIT group. This is the purpose behind the proposal for a satellite to fix the positions of sources with a precision of the order of seconds of arc, using lunar occultation techniques, raised by an ESRO Mission Definition Group in *Nature* recently (**228**, 756; 1970). In Britain the fifth satellite in the Ariel series, at present known as UK 5, is earmarked for X-ray astronomy and will probably be ready for launch in mid 1973. Somewhat more sophisticated than the Small Astronomy Satellite it will nevertheless have a similar positional accuracy. The design study was completed last autumn.

GALAXIES

New Local Group

from our Observatories Correspondent

IN 1968, Paulo Maffei discovered two faint, diffuse, objects in the Milky Way in the course of a survey at the Asiago Observatory in Italy with film sensitive to the near infrared. Maffei made no suggestion as to the nature of these objects. Now in the January issue of the *Astrophysical Journal Letters* (163, L25; 1971) a group of nine optical and radio astronomers at the Lick, Leuschner and Hale Observatories in California suggest that the brighter object, Maffei 1, is in fact a giant elliptical galaxy and moreover that it is possibly a member of the Local Group of galaxies.

Both of Maffei's objects are within half a degree of the galactic plane. As a result, they are heavily reddened and obscured by interstellar dust in our galaxy. The extinction of Maffei 1 in the visible is estimated to be 5 magnitudes (a factor of 100!) but in the near infrared it is much less. The California astronomers show that at 2.2 μ m the flux from the central 8" of Maffei 1 is comparable with that from a similar area in the centre of M31. After a correction for interstellar extinction the overall energy distribution of Maffei 1 is similar to that of the central bulge of M31 which in turn resembles the centres of giant elliptical galaxies. The spectrum of the object contains absorption features; for example, TiO bands and the sodium D lines. These features have the strengths characteristic of the nuclei of giant elliptical or Sa and Sb spiral galaxies.

Only crude limits are placed on the distance of Maffei 1. Its radial velocity is only 10 ± 50 km s⁻¹ relative to the Sun or 16.5 ± 50 km s⁻¹ relative to the centre of our galaxy. This velocity is too small to establish Maffei 1 as being necessarily outside the galaxy. Its extragalactic nature is established by two pieces of evidence. First, near infrared photographs show that it has the form typical of an E3 or E4 galaxy; moreover, the radial distribution of the surface brightness is more characteristic of an elliptical galaxy than the central bulge of the spiral. Second, it has the energy distribution characteristic of a massive galaxy.

Because the redshift of Maffei 1 is too low to use the Hubble constant, the Californian group has used dynamical arguments to estimate its distance. The mass-to-light ratio found typically for giant elliptical galaxies is thirty solar units. The internal velocity dispersion of the stars in Maffei 1 was estimated from the widths of absorption lines in its spectrum to be about 200 km s⁻¹. The mass-to-light ratio can be estimated from this quantity and from the observed brightness (corrected for interstellar absorption) of the object. The result is found to depend linearly on the distance; a value

of 1.2 megaparsecs gives a mass-to-light ratio of thirty. Its mass is then about 2×10^{11} Suns, comparable with the mass of the Milky Way.

Maffei 1 is thus about twice as far away as M31 and must be considered as a possible outlying, massive member of the Local Group. Maffei 1 has too much kinetic energy to be bound to the Local Group, however, unless it contains appreciable mass in the form of interstellar gas.

The Californians are continuing observations of Maffei 2. This is only 40' arc away from Maffei 1 and is implied to be also a highly obscured member of the Local Group of galaxies.

MOON

Lunar Quakes

from our Geomagnetism Correspondent

IN spite of the widespread publicity given to the rock samples returned from the Moon by Apollos 11 and 12, the most significant lunar experiment—the lunar seismic experiment under the supervision of Dr Gary Latham of the Lamont-Doherty Geological Observatory—continues to operate on the Moon itself. Seismometers were placed on the Moon by the Apollo 12 astronauts on November 19, 1969, as part of the Apollo Lunar Surface Experiments Package and since then have recorded a series of natural and man-made events. During the first seven months of operation, about 160 natural events were detected, of which at least twenty-six were small moonquakes. The rest were probably meteoroid impacts. In addition, seismic recordings were made of two man-made events—the impact on the lunar surface of the Apollo 12 Lunar Module (LM) ascent stage and the third

stage of the Apollo 13 Saturn booster (S-IVB).

Latham *et al.* report (*Science*, 170, 620; 1970) that, although the number of natural events was comparatively large, techniques for deriving the times and positions of these disturbances from their seismograms have proved discouragingly elusive. The evidence for the interpretation of some of these events as shallow moonquakes is thus circumstantial rather than analytical, but is none the less valid for that. For example, all of the supposed moonquakes occurred within three days of the Moon's closest approach to Earth during its monthly cycle; and at least one quake was associated with each monthly perigee. This strongly suggests that the release of seismic energy in the outer shell of the Moon is a result of the gravitational interaction between the Moon and the Earth, for the tidal strains thus set up are maximum at perigee. Even so, the moonquakes were small, the largest events having magnitudes between 1 and 2 on the Richter scale. Earthquakes of this magnitude would, of course, be barely perceptible. The low rate of seismic energy release on the Moon thus suggests that plate tectonics, and all that it implies, is not a lunar phenomenon.

But the most important data have come not so much from the natural events but from the two man-made disturbances—partly because the latter impacts were more energetic but chiefly because precise details of the sources were available. For one thing, body wave seismic velocities in the upper few metres of lunar material are very low indeed—0.1 km s⁻¹ for LM. To Latham *et al.* this is significant because such low compressional velocities were also obtained, by other workers, in terrestrial laboratory experi-

MIT's Second Look at Crab Pulsar

AT the height of the pulsar excitement in 1969 the X-ray astronomy group at MIT rapidly re-scheduled a rocket flight to see if they could pick up X-ray pulsations from the Crab pulsar to match the optical pulsations that had been recorded. They were just beaten by the NRL group, and the MIT flight carried out on April 27 from White Sands Missile Range became a valuable confirmation of the NRL data. *Nature* published a preliminary analysis of the MIT data a month after the flight (Bradt *et al.*, 222, 728; 1969), and the group's last word is being published in next Monday's *Nature Physical Science* (229, 40; 1971). Four groups altogether have now observed X-rays from the Crab pulsar (NP0532) with energies between 1 and 10 keV, but Rappaport *et al.* at MIT claim the greatest statistical precision with nearly a third of a million counts from the pulsar and the nebula around it.

Nothing in the new analysis contradicts what has already been published, fortunately, but Rappaport, Bradt and Mayer are able to present their conclusions on the parameters of the X-ray pulses more precisely by including all their data instead of only about half of them. They show that only 9 per cent of the 1.5–10 keV emission from the direction of the Crab is pulsed, and there is a substantial amount of emission after the main pulse occupying the valley preceding the interpulse, which is absent in the optical measurements. There are also significant differences in shape between the X-ray and optical interulses—and in fact the X-ray interpulse contains more energy than the chief X-ray pulse.

To round off the discussion the MIT group give their data on the spectrum of the pulsar at X-ray wavelengths, which one day will have to be fitted into a general theory of how pulsars work.

ments on returned Apollo 11 material. Moreover, the distance-travel time curves for the laboratory samples up to pressures equivalent to a depth of 20 km in the Moon (the limit of refraction for seismic waves from LM and S-IVB) had no sharp changes in slope, a property with which the spot body wave data from Latham's experiment are consistent. In other words, the limited evidence suggests that the distance-time curves for the upper 20 km of the Moon are also smooth up to about 6 km s^{-1} , which must mean that within that distance there is no major lunar boundary.

The other important result obtained by Latham *et al.* is confirmation that lunar signals have extremely long decay times—about an hour for LM and more than four hours for S-IVB. A comparable signal on Earth would die away in a few minutes. This suggests that lunar material has a Q (quality) factor as high as 3,000 (compared with 10–300 for the Earth's crust), possibly because of the lack of fluids in the Moon's outer shell. It seems likely, however, that other causes of the long reverberation times are also required. The two possibilities suggested are dispersion of the seismic waves, by which coherent waves propagate at different group velocities depending on their wavelength, or scattering, by which the path lengths of the waves are effectively increased by repeated reflexions at acoustic discontinuities.

Dispersion of surface waves requires the presence of a surface layer with a low velocity, which has been shown to exist. Scattering, on the other hand, implies the presence of heterogeneities in the outer shell of the Moon on a scale ranging from a few hundreds of metres to several kilometres, although surface irregularities may also be important. The existence of such heterogeneities has not been proved directly; but in view of the age of the Moon, the likely effects of meteoroid bombardment and the known low viscosity and high thermal expansion coefficient of at least some of the lunar material, such irregularities are not unlikely. At present it is quite impossible to decide between dispersion and scattering.

Latham's approach to the interior of the Moon is essentially experimental. Turcotte and Oxburgh (*J. Geophys. Res.*, **75**, 6549; 1970), on the other hand, take a more theoretical and speculative view. Their object is simply to deduce whether or not convection, such as that which is thought to take place in the Earth's mantle, can occur in the Moon. The difficulty is, of course, that convection probably depends on the heat produced by radioactive decay; and because the distribution of radioactive elements within the Earth is still a matter of disagreement, it is not very easy to make a reliable assessment of concentrations of lunar radioactivity.

Not to be deterred by this, however,

Turcotte and Oxburgh have calculated the uniform mantle concentration of radioactive elements which would produce the Earth's observed surface heat flow and then proceed to apply this figure to the Moon as a whole. They then use a reasonable theoretical model to show that under these conditions—that is, with an undifferentiated Moon—convection can occur even within a Moon having a thick rigid outer shell.

The problem is, of course, that the Moon cannot now be completely undifferentiated—the concentrations of radioactive minerals in the Apollo 11 rocks are almost certainly too high to be typical of the Moon as a whole. The question thus arises: is convection still going on in the Moon or has differentiation proceeded far enough to stop it? This, Turcotte and Oxburgh are not prepared to answer. According to their model, convective velocities would have to be two orders of magnitude higher than those in the Earth's mantle; and thus lunar differentiation would be complete in a few billion years. But it is difficult to tell what stage the process has reached.

Interstellar Silicate Extinction

THE demonstration by D. R. Huffman and J. L. Strapp in next Monday's issue of *Nature Physical Science* (**229**, 45; 1971) that the predominant feature in the ultraviolet region of the interstellar extinction curve, the peak near 2200 Å, could be an indicator of a silicate component of the interstellar grains rather than the "signature of graphite" should be a timely reminder to others searching for the chemical identification of the grains. The absence until now of an alternative identification can be traced chiefly to the lack of knowledge of the complex optical constants, over a wide spectral range, of commonly occurring materials. (Both the refractive index and the absorption coefficient are needed to carry out extinction calculations in which scattering and true absorption are included.) Extensive and precise spectral observations in the ultraviolet and in the infrared promise progress towards a unique identification; present indicators, such as the shape of the interstellar extinction curve, are too ambiguous, placing only rather broad limits on particle sizes and refractive indices. These opportunities will be largely wasted, however, unless sufficient research on the optical constants is carried out.

The 2200 Å feature is related to the lack of fundamental data. Following the discovery of this peak by T. P. Stecher in 1965 (*Astrophys. J.*, **142**, 1683) using rocket-borne detectors, Stecher and B. Donn noted (*Astrophys. J.*, **142**, 1681; 1965) that graphite had optical constants which could reproduce this detail in the extinction curve. Subsequent rocket

ORIGIN OF LIFE

Chemical Evolution

from a Correspondent

THE chemical origin and early evolution of life was the theme of a timely Nobel workshop at the Botanical Institute, University of Stockholm, on December 7 and 8, 1970. The timeliness results from recent publications and theories propounded by the four eminent speakers who delivered the invited public lectures which preceded round-table discussions.

Dr C. Ponnamperna (NASA, Ames) introduced the subject with a survey of the geochemical history of the Earth and the theories advanced to account for the origin of life, culminating in the classic writings of Oparin (1924) and Haldane (1928) which set the stage for all modern research on primordial organic chemistry. The range of compounds which can be synthesized under simulated conditions of the primeval Earth, using varying sources of energy, is impressive—these include, for example, most of the proteinoid amino-acids, simple peptides,

flights and observations from the Orbiting Astronomical Observatory have confirmed the existence of the feature and, in addition, have defined its wavelength more precisely. K. Nandy and H. Seddon (*Nature*, **226**, 63; 1971) have found from the most recent evidence that the match of the observed and predicted peaks is not good, the difference being outside the present errors of observation. Nevertheless, since 1965 considerable importance has been attached to the original identification and the feature has been accepted as the "signature of graphite". It should be pointed out, however, that in 1965 graphite was already a candidate for the grain material; theoretical arguments had suggested the possibility of condensing graphite particles in the cool atmospheres of relatively carbon-rich stars. The confirmation of the ultraviolet peak was therefore important.

Huffman and Strapp have now shown that silicates can also produce this peak. Their interest in the silicates was prompted by other spectral evidence in the infrared (where optical constants are again needed) and by theoretical calculations of the condensation of silicates in cool stellar atmospheres. They had to measure the complex optical constants, as none previously had been determined. Further laboratory observations of many materials in the infrared and ultraviolet will be needed to strengthen this identification and to determine whether it is unique. It is to be hoped that this work by Huffman and Strapp will stimulate greater efforts to determine the optical constants of the wide variety of materials.

nucleotide bases and nicotinamide.

Professor M. Eigen (Göttingen) then advanced his recently developed theory of evolution during the phase of self-organization after chemical evolution had occurred and before Darwinian evolution began. This physical theory of evolution, starting at the molecular level, stresses the close linkage between the process of the recognition of the information properties of nucleic acids and the functional properties of proteins—information acquires a meaning only when coding for function, so that feedback processes occur between both information and function. Thus self-duplicating systems could not have been random but must have been directed.

Eigen has developed an equation which has the properties of selection, for it includes a value factor which would decide which molecular species would be selected to grow and which to decay. The equation is interesting because it has a vectorial function which would select not just for a single molecular species but for many, so resulting in more and more coupling. But there is also a moving threshold value, so that more and more species would be below the threshold value and thus decay, which means that the autocatalytic properties of the system would take care of selection. The equation also recognizes that the system cannot be at equilibrium because the growth properties would then disappear; however, the steady state of the total system must be constant with “fluxes” and “forces” to maintain the state. Briefly, the theory includes the ability of competitive growth and selection, sharp selection, evolutionary development from the initially established cycle (the universal code) and selection against “parasites”.

Professor I. Prigogine (Brussels) talked on instabilities and structure and explained the phenomena of natural boundaries using models from hydrodynamics and the Jabotinski reaction (oxidation of malonic acid in the presence of cerium ions). Instabilities are created at boundaries resulting in “dissipative” chemical structures which can be stable for some time before abruptly disappearing. Professor Prigogine developed the idea that the dissipative structures occur at conditions which are far from equilibrium, thus favouring autocatalysis.

Dr S. Spiegelman (Columbia, NY) emphasized that nucleic acids are the only molecules which can duplicate themselves and have the possibility of transmitting errors, these being the two prime requirements for directed evolution of living systems. He discussed his work on Q β replicase and the search for variants with low molecular weights. Variants had been obtained which had discarded 85 per cent of their molecule leaving only a strand of about 550 nucleotides. These variants could adapt

to certain changes in environmental conditions by altering the allostery of their enzymes. Recently, mini-variants containing only 180 nucleotides have been obtained which can now be made to add about fifty nucleotides to themselves.

TUMOUR VIRUSES

A Transforming Gene

from our Cell Biology Correspondent

A LONG expectant audience has received its reward; in the latest issue of the *Proceedings of the US National Academy of Sciences* (67, 1775; 1970), Dulbecco and Eckhart report some of the properties of *ts3*, a mutant of polyoma virus isolated by M. Vogt, with a temperature sensitive lesion in one of the transforming genes of this virus. Polyoma virus and the other small DNA tumour virus, Simian Virus 40, can infect certain cells and cause them to be stably transformed so that their phenotype resembles in many respects that of tumour cells. These two viruses contain only 3×10^6 daltons of DNA sufficient to code for about 200,000 daltons of polypeptide or six to eight proteins.

On the face of things it should be straightforward to define such a simple genome, including those genes responsible for the establishment and maintenance of transformation, by isolating temperature sensitive mutants. An understanding of the molecular mechanisms of

virus transformation should also throw light on the essential differences between normal and cancerous cells. In 1965 Fried isolated the *tsa* mutant of polyoma virus which carries a temperature sensitive lesion in a gene required for the establishment but not the maintenance of transformation. But we have had to wait five years for the characterization of a mutation in a polyoma gene which controls the maintenance of transformation.

Hamster cells of the BHK line transformed by *ts3* and maintained at the permissive temperature, 32° C, have all the characteristics of BHK cells transformed by wild type polyoma virus; unlike untransformed cells, *ts3*-BHK cells grow in agar, are not subject to topoinhibition, that is, the inhibition of cell cellular DNA synthesis by such factors as the proximity of other cells, and their serum requirement differs from that of untransformed BHK cells. When *ts3*-BHK cells are shifted from 32° C to 39° C, however, although the cells' ability to grow in agar and their serum requirements are unchanged they become sensitive once again to topoinhibition. BHK cells transformed by wild type virus, by contrast, are insensitive to topoinhibition at both temperatures. This indicates that the loss of topoinhibition, which characterizes transformation by polyoma virus, depends on the continued production of a functional polyoma-gene product.

Optical Frequency Breakdown in Gases

ONE of the most surprising effects produced by powerful laser light is that it can transform gases which are normally transparent to the long wavelength red and infrared radiation of lasers into opaque, intensely bright and highly conducting plasmas in times ~ 1 ns. If the laser light is very powerful, say ~ 10 GW obtainable from multistage oscillator amplifier systems, a series of small discrete plasma regions separated by centimetres extending over several tens of metres along the unfocused beam can readily be produced in air at atmospheric pressure. Focused beams from much less powerful single stage lasers, giving intensities around 10^{11} W cm $^{-2}$, can also create multiple collinear plasmas, but on a very much smaller scale extending over millimetres; the newly discovered high pressure CO $_2$ lasers, the so called TEA (Transverse Excitation, Atmospheric) devices, operating in the infrared, can cause optical frequency breakdown of gases at smaller intensities.

There has been much discussion about the mechanisms responsible for discharge initiation and the processes which lead to the subsequent growth of ionization and the nature of the complex plasmas formed. Some recent research into the phenomenon is reported by W.

Zernik in next Monday's *Nature Physical Science* (229, 46; 1971). The laser flash itself evidently releases the first electron from a gas atom even though the value of the quantum of energy associated with the light is typically, for a ruby laser, only 10 per cent of the ionization potential. This seems to imply a multiphoton absorption mechanism which is considered by many as a satisfactory explanation of initiation (H. B. Bebb and A. Gold, *Phys. Rev.*, 143, 1; 1966), but accepted only with reserve by others (R. G. Tomlinson, *Phys. Rev. Lett.*, 14, 489; 1965).

Another surprising feature is the success with which an extrapolation of the classical microwave breakdown theory of gases to optical frequencies can account for many of the observed phenomena. The extrapolation is based on the view that ionization growth and plasma formation occur, following initiation, by inelastic collisions between atoms and electrons in which the interaction energy is drawn from the electromagnetic field of the laser light. This at once leads to the concept of an effective electric field, oscillating with the optical frequency, which produces the same energy transfer between electrons and atoms as a static field to which it is related by the light

frequency ω and electron-atom collision frequency. By this means excitation, ionization and other transport properties, readily measurable under static fields, may be used to deduce optical frequency counterparts. In this way it is possible to derive expressions for the critical radiation intensity required to cause breakdown in gases exposed to laser light; it turns out to be approximately proportional to ω^2/τ where τ is the duration of the laser flash (F. Morgan, L. R. Evans and C. G. Morgan, *J. Phys. D.*, **4**, in the press).

Comparison between measurement and prediction is remarkably good when the experimental complexities and theoretical approximations are taken into account, but it has been argued that because the classical oscillation energy of the electron in the laser field is small compared to the photon energy the classical description is inapplicable.

Zernik contends that this reasoning is incorrect and he applies a simple extrapolation of the classical theory in the case of breakdown in helium with some success over a wide pressure range.

The *ts3* mutation also affects the response of permissive cells supporting the replication of the virus. Usually when polyoma virus replicates in mouse cells, host DNA synthesis is induced concomitant with the replication of the viral genome and the cells are induced to move. At 32° C the *ts3* mutant behaves in these respects like wild type virus, but at 39° C both the induction of cell movement and cell DNA synthesis by *ts3* are impaired. It seems unlikely that the *ts3* gene product directly controls all these responses in both transformed hamster cells and lytically infected mouse cells. More likely the *ts3* gene may specify a molecule which changes the chemistry of the surface of the infected cell. Dulbecco, Eckhart and Burger have evidence (as yet unpublished), that this is indeed the case, but that is another story about which we shall no doubt shortly be reading.

Apart from inducing cellular DNA synthesis, polyoma virus and SV40 replicating in permissive hosts induce the scission of the cell's genome and as a result pieces of cellular DNA of appropriate size are enclosed in capsids of the virus. The possibility that such pseudovirions, as they are called, might be useful as vehicles for the transduction of cells has been widely and often uncritically discussed. The analogy between pseudovirions and certain transducing phage particles remains, however, and Grady, Axelrod and Trilling (*Proc. US Nat. Acad. Sci.*, **67**, 1886; 1970) are among the groups pursuing the possibility of showing transduction of eukaryotic cells. They report that the pseudovirions produced when SV40 replicates in the VERO line of monkey cells contain repeated and unique sequences of monkey DNA in the

same proportions as in the total VERO cell genome. This indicates, of course, that particular portions of the genome are not preferentially incorporated into pseudovirions. There is therefore no hope of using pseudovirions as analogues of lambda phage for specialized transduction, that is, the transduction at high frequencies of specific portions of a cell's genome. A putative general transducing potential remains, however, and Grady *et al.* have been able to show that about 10 per cent of the SV40 pseudovirions taken up by mouse embryo cells enter the nucleus carrying their monkey DNA undegraded. Whether such foreign DNA is replicated and expressed, however, is the crucial question which remains unanswered.

AAAS

Model Biology

by our Special Correspondent

THE increasing infiltration of biology by physical scientists and mathematicians was plainly reflected in the contribution of the American Mathematical Society to this year's meeting of the American Association for the Advancement of Science (AAAS) in Chicago. The section was devoted entirely to biology; in particular to two of its most fascinating and intractable problems—control of development and central nervous function.

Dr B. C. Goodwin (University of Sussex) gave a somewhat apologetic talk

Synthesis of Bacterial Cell Walls

FUNCTIONS for the teichoic acids of Gram positive bacteria are proposed in three articles in next Wednesday's *Nature New Biology* (**229**, 1971) by a team in the Microbiological Chemistry Research Laboratory at the University of Newcastle upon Tyne. Teichoic acids are polymers composed either of glycerol phosphate or ribitol phosphate, and the principal chain has substituents on it which vary in different strains and include D-alanine, D-glucose, D-galactose or amino sugars. The Newcastle team (J. Baddiley *et al.*), who first discovered these polymers, suggested in 1961 (*Nature*, **191**, 570) that they participate in ion-exchange reactions in the outer regions of the bacterial cell; the phosphate of the teichoic acids bestows on the isolated cell walls the ability to bind magnesium ions. Baddiley *et al.* have now isolated functioning cell wall-cell membrane fragments and cell membrane fragments without any cell wall. These fragments catalyse the synthesis of teichoic acids from UDP-glucose and CDP-glycerol and require high concentrations of Mg^{2+} ions. Pre-incubation of the fragments of wall membrane made the membrane enzymes independent of Mg^{2+} concentration; the pure membrane fractions required 10 mM Mg^{2+} for maximal activity. This is a direct demonstration of the function of teichoic acids in binding Mg^{3+} ions and making them available to the membrane.

Chloramphenicol inhibits the biosynthesis of the teichoic acid of a bacterial cell wall in a cell-free system of fragmented cell membrane from *Bacillus subtilis*. The chloramphenicol seems to inhibit the synthesis of the teichoic acid directly and is unrelated to protein synthesis. The antibiotic inhibits the transfer of glucose from UDP-glucose to the polymer. The inhibition is specific for glucose and does not occur with other nucleotide sugars. The polymer, whose synthesis is inhibited, is unusual in that the glucose is

in the principal chain, rather than attached to it.

The biosynthesis of several bacterial wall polymers uses lipid intermediates that aid in the transport of sugar residues and related components from intracellular nucleotide precursors through the membrane to the polymer chains in the wall. Such lipid intermediates are used in the biosynthesis of both teichoic acids and peptidoglycan, which is a polymer containing N-acetylmuramic acid, N-acetylglucosamine, alanine, lysine, glutamic acid and glycine.

The Newcastle group has further examined the possibility that a single lipid may be common to both pathways, and that therefore the availability of this lipid could play some part in the regulation of cell wall synthesis. The amount of these lipids in bacteria is very small and their direct study is therefore difficult. Consequently, Baddiley and his colleagues looked for an indirect answer. If in a single organism the identical lipid is involved in the synthesis of the two polymers, competition for the limited amount of lipid would probably occur. They therefore examined the relationship between the biosynthesis of peptidoglycan and teichoic acid in cell membrane fragments from *Staphylococcus lactis* I3. Inhibition of teichoic acid synthesis is achieved by the addition of peptidoglycan precursors. The antibiotics bacitracin and vancomycin inhibit the formation of peptidoglycan and prevent the return of the lipid intermediate to the pool; the antibiotics have no direct effect on teichoic acid biosynthesis. When peptidoglycan precursors and the antibiotic are added together, however, thereby effectively trapping the lipid intermediate, a sharp inhibition of teichoic acid synthesis results. It follows that the same lipid carrier molecules are used for transporting precursors of both peptidoglycan and teichoic acid.

on his analysis of the studies of Gaze and his co-workers on the formation of retino-tectal connexions in amphibians. This work has shown that connexions are formed along two developmental axes—dorso-ventral and naso-temporal—determined at different stages in the growth of the tadpole. Goodwin pointed out that the diffusion model with “morphogen” gradients proposed by Gaze *et al.* (*J. Physiol.*, **165**, 484; 1963) does not account for all the experimental data from their work with compound eyes. In particular, there is a mysterious kink which appears in one of the axes when a “double ventral” eye is created by grafting the ventral half of one retina to that of the other at a stage of development between the determination of the two axes.

Goodwin went on to show how this distortion could be explained in terms of a model of development based on frequency gradients in periodic signals propagating across the embryonic field (B. C. Goodwin and M. H. Cohen, *J. Theoret. Biol.*, **25**, 49; 1969). Assuming signal sources at 90° to each other, the model predicts an interaction between the two axes which would produce the observed kink. Goodwin pointed out, however, that any model with two interacting axes 90° apart would equally explain this finding. The specific model he used could only be vindicated by further research showing periodic movements of the developing cells.

No such diffidence characterized the presentation of Mr A. D. J. Robertson (University of Chicago), who has interpreted, from the mass of literature and films, the aggregation of the cellular slime mould *Dictyostelium discoideum*. Although the life cycle of this organism, which entails the formation of a slug from initially independent amoebae, provides a beautifully simple developmental paradigm, it has so far eluded explanation. Robertson's dogma was that not only could a model with frequency gradients in periodic signals elegantly explain many of the bewildering observations on slime mould aggregation, but periodicity and pulsatile movement of the amoebae could actually be seen on film. After describing the aggregation of *D. discoideum* in the conceptual framework of a mathematical model developed in collaboration with Professor M. H. Cohen (*J. Theoret. Biol.*, in the press), he went on to illustrate his points with just such a film; and concluded with the reassurance that if the phenomena he wished to emphasize were not immediately convincing, this was because real conviction could only be acquired after repeated observation with a closed mind.

The contribution which followed underlined the unfortunate truth that it is not difficult to make models: the difficulty lies in finding the right one. Dr L. A. Segel (Troy Polytechnic Insti-

tute) approached the problem of slime mould aggregation as an expert on heat equations. Points of agreement with the Robertson-Cohen doctrine were apparent: aggregation is guided by chemotaxis, for which the attractant (acrasin) is cyclic adenosine monophosphate (cyclic AMP), secreted by the amoebae along with an enzyme (acrasinase) which rapidly destroys it. But whereas the model of Cohen and Robertson depends on the assumption of essentially pulsatile production of cyclic AMP, that of Segel assumes that production is continuous. His amoebae aggregate where random movement has resulted in chance clusters in which the concentration of cyclic AMP is too great to be efficiently destroyed by the acrasinase.

Dr R. B. Stein (University of Alberta), speaking on the properties of neuronal spike trains, based his conclusions on the behaviour of a concrete or, more precisely, an electronic model. He used the response of a model neurone to sinusoidal stimulation, with and without random background noise, to illustrate a possible adaptive function for random variation in the nervous system. With low frequency stimulation and no background noise, the impulse response tended to be phase locked (as in the real auditory system); but with increasing frequency,

both phase and frequency information were lost because the firing frequency of the neurone is limited by the time course of membrane capacitance discharge. With added noise, however, the membrane is maintained close to threshold; and when the response is averaged over time, the probability of firing of the neurone emerges as a fairly precise function of the input. Thus by averaging over neurones instead of over time, a reliable response can be seen to be produced from a noisy system; and further support is provided for an idea that is far from new to brain research.

The usual justifications for model making in biology are that it is necessary for a proper understanding of complex systems, and that it makes possible quantitative predictions which can be rigorously tested. Dr B. Julesz (Bell Telephone Laboratories) must be the only living theoretician who can also claim to have created a spectacle whose visual impact unfailingly causes non-specialist audiences to gasp aloud. His talk on his experiments in binocular depth perception with computer-generated random patterns was liberally illustrated with slides and films from which proof of his theory literally leapt out. There was no need for Julesz to labour his point: seeing is believing.

Fusing Cells in Mice

INNUMERABLE experiments have now been performed to fuse together diverse types of cell *in vitro* by using inactivated Sendai virus. The hybrid cells produced by fusion of two normal cells possess a joint cytoplasm, but retain, for a while, the individual nuclei of the parent cells (although these may subsequently fuse to form one nucleus). One of the most interesting aspects of hybrid cell formation is that a cell with a defect in, for example, some enzyme activity can be “cured” by fusion with another cell type which contains the missing activity. A new and rather complicated way to test for this “gene complementation” is reported by N. L. Levy and R. L. Ladda in next Wednesday's issue of *Nature New Biology* (229, 1971).

“Old” mice and “new” mice differ at only one genetic locus, which specifies a protein which confers haemolytic complement activity on the animal. “Old” mice can have haemolytic complement activity restored by the injection of bone marrow cells from the “new” strain and this activity probably results from migration of the injected cells to the spleen, where they elaborate the missing protein. Levy and Ladda have used the restoration of haemolytic complement activity in a “new” mouse injected with hybrid cells as a test to see whether the hybrid cells can make the missing protein activity.

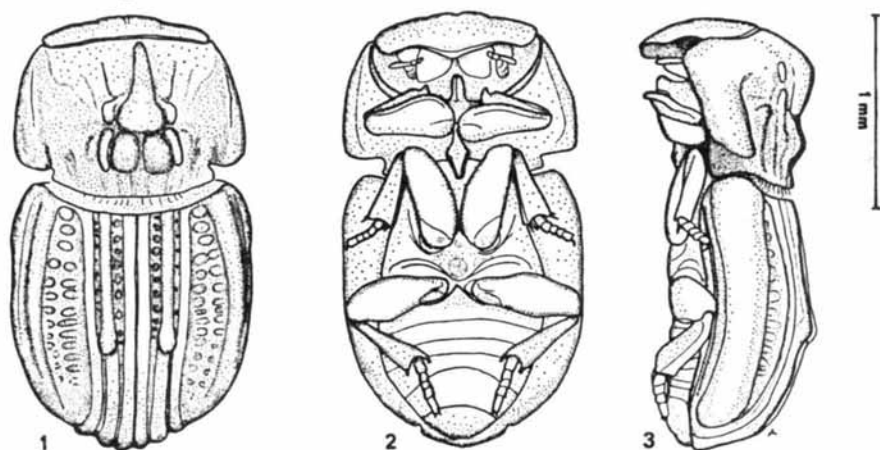
Hybrid cells were made by fusing

together different types of mouse or chick cells by the usual treatment with Sendai virus. The injection of “new” mouse kidney: “old” mouse spleen or “old” mouse spleen: chick erythrocyte hybrids restored haemolytic complement activity to deficient mice. This result means that the hybrid cells must be able to synthesize the gene product in which the new mice are defective. This is not too surprising in the former case, because one of the parent cell types derives from “new” mice which have the activity. The other result cannot be explained in this way, however. Because little chick cytoplasm is incorporated into chick erythrocyte: mammalian cell hybrids, it seems likely that it is the presence of the chick nucleus in the second set which enables the hybrids to make the missing complement activity.

There seem to be two ways in which this could happen. Levy and Ladda do not know whether the missing activity was filled by a chick protein (which would be specified by the chick nucleus but be able to perform the same catalytic functions as the mouse-specified protein), or whether the hybrid can make the mouse protein itself. The former could result from activation of the chick nucleus in the hybrid cell. The alternative explanation would imply that the mutation which causes the “old” mouse phenotype affects a control gene and not the structural gene which codes for the missing enzyme.

ENTOMOLOGY

Termitophilic Beetle



A bizarre, flightless and blind scarab beetle, only 2 mm long, has been found by J. Krikken in the Wasmann Collection in the Natuurhistorisch Museum at Maastricht. The beetle, shown here, had passed unnoticed in the museum since the beginning of this century when it was collected by N. Holmgren from a termite nest in the mountains of south-eastern Peru. Its affinities seem to be obscure, but Krikken (*Proc. K. Ned. Akad. Wet.*, C, 73, 469; 1970) describes it as a new genus and species (*Termitaxis holmgreni*) in the aphodiid tribe Rhyparini. The illustration shows (1) dorsal, (2) ventral, and (3) lateral views.

BEHAVIOUR

Labour Rewarded

Experimental Psychology Correspondent

IT might be supposed that when an animal is offered the choice between working for food and being given it without working, other things being equal it would choose the latter. Indeed, the assumption it would choose the less laborious alternative underlies a good deal of theorizing about learning in animals. The appearance recently of two reports which indicate that animals seem to prefer to work for food may therefore be surprising.

In the first article (*Science*, 166, 399; 1969), A. L. Neuringer had shown that pigeons would peck keys and rats would press levers to obtain food although exactly similar food was freely available in a food cup in the experimental chamber. D. Singh now shows that rats still prefer to work even when the amount of work is increased, and even when working provides food less quickly than when it is not worked for (*J. Comp. Physiol.*, 73, 320; 1970).

In Singh's experiments rats accustomed to being fed for only 1 h per day were trained on alternate days either to work for food by pressing a lever, or to receive it free at the same average rate. In subsequent tests with the free food at one end of the experimental box, and the food to be worked for simultaneously present at the other end, rats showed high and consistent preferences for working. Ten rats which were required to make one lever press per pellet of food gained an average of between 78 and 94 per cent of their food by working on each of the four days of preference testing. Even

when required to make eleven presses per pellet, rats' preferences for food gained by working did not fall below 67 per cent on any of four test days.

In a further similar experiment rats, instead of acquiring free food at the same

mean rate as they had achieved in their previous working session, were put at a disadvantage by working, because they received food 12.5, 25 or 50 per cent faster by accepting it free. Only in the last of these conditions did the animals' preferences switch to free food.

Singh also presents an experiment in which children obtained marbles either free or by pressing a lever for them; and again working was preferred. He interprets his data as meaning that animals (including children) prefer to be in control of their environment. Though this argument has a certain force, particularly in relation to his own experiments in which rats not working for food had to wait for each pellet to arrive, a situation that may in itself be frustrating, his explanation seems less apt when Neuringer's results are considered. In that situation animals had a pile of free food available, and were perfectly in control of whether they ate it or not.

The sources of this motivation to work, or to do something which is instrumental to gaining access to food, thus still seem obscure, though it is obviously important for any theoretical analysis of motivation that they be recognized. This is, however, exactly the kind of experimental result which could appeal to the imagination of those persons who are becoming famous for their fanciful extrapolations from animal to human behaviour.

How a Virus Assembles

KLUG and his colleagues have three papers in next Wednesday's *Nature New Biology* (229, 37; 1971) in which they have gone no small way to defining the sequence of events in the assembly of tobacco mosaic virus. It is known that the protein alone can generate virus-like particles with helically arranged subunits. It can also under marginally different conditions form superficially similar rods, which are, however, made up of stacked disks, each containing seventeen protein subunits. The important new discovery is that a stable intermediate exists in the process of assembly to normal helical particles, and that this is a double disk, with two layers of seventeen subunits. In order to generate the helical particle these disks have to dislocate to a "lock washer" form. A transition between washer and lock washer evidently comes about in response to a change in pH, when two ionizing groups in each subunit become masked. These can be identified with the anomalous carboxyl groups recognized by Caspar in the intact virus.

The double disk is evidently the basic entity in the polymerization process, and its formation from smaller pieces is rate determining. This may be compared with the rate-determining formation of an oligomeric nucleus as the first step in many biological association processes,

the ensuing polymerization on these "seeds" then being rapid. The growth of the TMV particle is greatly accelerated by the presence of its endogenous RNA, but only when the protein is already present as preformed double disks. When, on the other hand, the protein is in the "disaggregated" state, which in fact consists of small aggregates, and in particular a high proportion of trimers previously suspected to be the polymerizing unit the formation of helices remains very slow. With disks the growth of virus particles is complete in minutes. The RNA evidently recognizes the protein in the first disk, and thereafter disks are progressively added. The vital RNA recognition site is in the 5' terminal region, for after treatment with spleen exonuclease, which degrades from the 5' end, the rate of particle growth is greatly retarded. Degradation at the 3' end with venom enzyme by contrast has little effect. It is important biologically, Klug *et al.* suggest, that the "relaxed" associated form of the protein is the disk. If the pH and salt concentration are not allowed to deviate greatly from the putative conditions prevailing in the cell, it is only in the presence of the RNA that the equilibrium is displaced towards the lock washer form as a step in the helical association.

NUCLEIC ACIDS

Ribosomes Revived

from our Molecular Biology Correspondent

"THE recognition of specific nucleotide sequences by proteins represents one of the more fundamental molecular processes in the biosphere." Teilhard de Chardin calling from the great beyond? By no means: it is Schaup, Green and Kurland who get their paper (*Mol. Gen. Genet.*, **109**, 193; 1970) off to a flying start with this intoxicating declaration. They then go on to describe how some of the proteins of the 30S ribosome of *Escherichia coli* will under defined circumstances bind only to their allotted sites on the 16S RNA, and they imply that, because RNA sequencing is now a routine skill, the auguries for determining the sequence of specific protein binding sites on the RNA are excellent.

It is known from the work of Nomura's group that the primary step in reassembly of the 30S particle involves the binding of only a handful of "core" proteins to the RNA, and this is borne out by the work of Schaup *et al.* who find that only five out of the sixteen 30S proteins that they tried were able to form defined complexes with the 16S RNA in a medium of high salt concentration containing 0.02 M magnesium. The conditions are important, for at lower concentrations the association is obscured by the kind of non-specific binding expected between RNA and any moderately basic protein. The combining ratios of RNA and each individual protein can be determined by incremental addition of labelled protein, and measurement of the amount of protein associated with the RNA after separation from unbound protein by sucrose gradient centrifugation, gel filtration or electrophoresis. Of the five proteins displaying strong binding, four show unquestionable saturation at 1:1 and one has undefined stoichiometry. To show that each protein enters a unique site, competition experiments were performed, in which the binding of a ^{14}C -labelled protein was measured in the presence of tritium-labelled proteins. There was no competition except when the additional protein was the same species as the binding protein. Instead, however, there was clear evidence of enhancement of binding of some proteins by others. This cooperative element was to be anticipated from Nomura's results. Some discrepancies between his classification of the proteins into binding and non-binding categories and those of Schaup *et al.* are put down to conformational or oxidative damage on standing. There is also an allusion to evidence of interaction of two 30S proteins with the RNA from the 50S particle, and this may relate to the finding of Nomura's group that the reassembly of the 50S particle is promoted by

the presence of intact 30S subunits.

A prominent feature of the reconstitution process is that it requires transient exposure to a higher temperature. This is a condition for correct refolding of an unfolded or incorrectly folded intermediate. That more subtle manifestations are also involved is now shown by Miskin, Zamir and Elson (*J. Mol. Biol.*, **54**, 355; 1970), who have examined the requirements for peptidyl transferase activity in the 50S ribosome. This is assayed by Monro's procedure whereby, in the presence of high concentrations of alcohol, formylmethionine is transferred from fMet-tRNA to puromycin. The reaction, it turns out, is characterized by an absolute requirement for monovalent cations, of which ammonium and rubidium are the most effective, potassium nearly so, and sodium and lithium do not work. Magnesium must also be present. The ribosome can be reactivated by adding the monovalent cations back, but this reactivation is vanishingly slow at low temperature, whereas it takes only a few minutes in the neighbourhood of 40°C. The reactivation is first order, but shows a bent Arrhenius plot, which may reflect conformational adjustments. In terms of sedimentation and optical characteristics the activation involves no gross change in structure, and may

therefore be highly localized. The authors note that under the standard conditions of assay reactivation will occur, so that the assay must be conducted at low temperature in any search for an equilibrium between active and inactive states.

That such considerations may have a much wider relevance than has been envisaged hitherto is suggested by the accompanying paper from the same laboratory (Vogel *et al.*, *ibid.*, 379), which demonstrates the existence of a similar temperature-dependent transformation in 30S ribosomes, assayed in terms of poly U-stimulated phe-tRNA binding. More particularly, streptomycin will bind to the 30S ribosome only when it is in the active form. This binding is immeasurably fast, and the slow binding process observed by earlier workers is thus to be explained in terms of rate-determining reactivation at the temperature of the measurements. Three antibiotics that operate on the 50S particle follow the same pattern: binding occurs only when the ribosome is in its active state. What delicate structural disturbance might control the activation equilibrium it is scarcely useful to speculate, but these results might give a number of workers in the field cause for deep reflexion.

Floating to Synchrony

BIOCHEMISTS who are clamouring after synchronous cultures of mammalian cells, for without them it is extremely difficult if not impossible to define the changes in a cell's biochemistry during the normal cycle of cell division, should be heartened by a report in next Wednesday's *Nature New Biology* by S. Shall and A. J. McClelland (**229**, 1971). These workers claim that synchronously dividing populations of LS cells, a line of L cell mouse fibroblasts which grows in suspension, can be obtained by carefully layering an unsynchronized population of cells at the top of a column of complete culture medium, and, after leaving the column for 50 min at 37°C, by removing the top millilitre. The cells recovered in this millilitre layer, about 2.25 per cent of the initial load, prove to be in the premitotic (G2) or very early mitotic stage of their growth cycle. In short, many, if not all, LS cells at these stages in the cycle float in conditions in which cells at other stages sink. This method has the great attraction of remarkable simplicity and speed, especially by comparison with the other techniques currently used for synchronizing cell populations: for example, sucrose gradient centrifugation, manipulation of the concentration of serum in the cell's medium and the physical detachment of mitosing cells.

Shall and McClelland's method is in many respects similar to the so-called

"staput" gradient procedure exploited by Miller, Phillips and their colleagues in Toronto (*J. Cell Physiol.*, **73**, 191; 1969). It apparently relies on natural gravity to separate cells on the basis of their size rather than their density, but whereas the Toronto group added bovine serum albumin to stabilize their gradients Shall and McClelland, after first experimenting with sucrose gradients, found that they could dispense with such additives. At least with LS cells separation can be achieved in the same medium in which the cells are routinely cultivated.

Any technique which minimizes the changes in the medium of eukaryotic cells is an advance because the fickle behaviour of such cells and their sensitivity to changes in the composition of their medium are notorious. Serotonin, for example, as Boucek and Alvarez report in the same issue of *Nature New Biology* (**229**, 1971), alters the behaviour of several lines of human and murine fibroblasts although it has no detectable effects on other types of cells. In the presence of serotonin, subcultures of these fibroblasts start multiplying some 6 h sooner than control cultures in a medium lacking serotonin. This substance apparently accelerates the attachment of fibroblasts to their culture vessels, but that is not the whole story, for serotonin also increases the viability of fibroblasts during tissue culture.

Cycles in Social Behaviour

by

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Systematic study of social behaviour in terms of time may bring to light patterns worthy of investigation. For this, a terminology is needed, and some physical terms might usefully be applied to sociology.

SEQUENCES that are repeated again and again are as obvious in the social behaviour of human beings as in the physiological behaviour of organisms. They have been studied extensively in the one case and not the other. One generation of biologists has followed another in noticing the phasing of the rhythms of life to such astronomical influences as the rotation of the Earth, the orbit of the Moon about the Earth, and the orbit of the Earth about the Sun. They have repeatedly produced and pondered over descriptions like that by Brown of fiddler crabs in their intertidal habitat. "The crabs spend much of their lives in burrows that they dig for themselves, but as each tide ebbs and exposes the burrow entrances the crabs come milling out to feed. While the times of foraging for food vary rhythmically with the tides the crab's skin colour varies with time of day. As the day dawns the crabs darken and as the Sun sets they become pale."¹

Many cyclic phenomena in society are also related to astronomical events, and some of them have been for long stretches of time. In Britain there are, for example, three principal ways of reckoning the beginning of "a year" and three sets of associated cycles. There is first of all the official financial year. The year in ancient Rome began in March (hence September, October and so on). March 25 was for a long time the beginning of the financial year; it was at the point in what had once been the first month which more or less coincided with the vernal equinox, which is as good an astronomical peg for the new year as the winter solstice. The start of the financial year was shifted forward into April when England finally accepted the Gregorian Calendar in 1752 and had to subtract eleven days from the year in order to fall in line with Europe. Hence the Chancellor of the Exchequer usually comes out to introduce his Budget on a Tuesday (which is the traditional day, just as Thursday is the traditional day for altering the bank rate) in April soon after the closing of the previous financial year.

Second, there is the civil or calendar year, which is also of Roman origin. One of Julius Caesar's predecessors added two more months, January and February, to the year, and Caesar himself confirmed that the calendar year should begin on January 1, and incidentally gave his name to the month which had until then been called Quintilis. The guidance came as much from the Moon as the Sun. "Caesar was swayed by the fact that the date happened to be the day of the occurrence of the new Moon following the winter solstice of the preceding year."² It was particularly appropriate because January took its name from the two-faced Roman god, Janus, who presided over the beginnings of all enterprises and events and who

was there to be seen in sculpted form over the entrances to Roman houses.

And third, there is the academic year. Its origins are obscure. The standard explanation is that no mediaeval student could take up residence until he had helped to gather in a harvest which had to wait on the Sun. Whatever its origin, the academic year is clearly of great import, affecting as it does not just the round of events in colleges and schools but also the timing of the peak holiday period for parents and others in the summer.

Need to follow Biology

Without behavioural sequences strictly geared to years like these, to months and to days, and also to the week as a time interval without an astronomical tie; and without hundreds of others which are not regulated by the common calendar of society, the social order could scarcely exist. But sociologists have not yet imitated the biologists; they have hardly begun to describe, let alone to analyse, these sequential chains of recurrent behaviour which are sufficiently similar (in spite of the element of uniqueness about the form which the behaviour takes on each occasion) to justify talking about recurrences. In this respect, a great deal more is known about fiddler crabs than about chancellors of the exchequer or vice-chancellors of universities.

The omission should surely be remedied. Time is no less important as a coordinate for social than it is for biological or physical phenomena. Though the sense of duration of time varies from person to person and minute to minute, it is almost universally agreed that time does "pass" and that it is more precisely measurable than most of the other variables which have engaged the attention of sociologists. Systematic study of social behaviour in terms of time may bring to light various patterns which would merit investigation.

If this hope is to be realized, attention must be given to terminology. Without a set of terms it is difficult to discuss the subject at all, let alone to decide what may be worth observation or measurement. Classical physics and applied mathematics provide a very extensive set of such terms, some of which have been borrowed and found useful in biology³. Our question is whether this kind of language could also serve in sociology. In an attempt to answer this question, we suggest a terminological scheme, with examples of specific usages in various social contexts which indicate the kind of general approach to the subject that might be fruitful. The words in italics are those for which definitions are suggested. The meaning of the terms suggested is also illustrated in the attached diagrams.

We first consider three different mathematical characterizations of the time coordinate, moving from the less to the more sophisticated, which correspond in a very general way to historical developments in conceptions of time as an objectively measurable quantity. (There is an excellent review of historical changes in the concept of time in ref. 4, which consists of papers delivered at the first conference of the International Society for the Study of Time.) We then consider some temporal patterns of behaviour at three different levels of social organization. In each case the more complex includes within itself

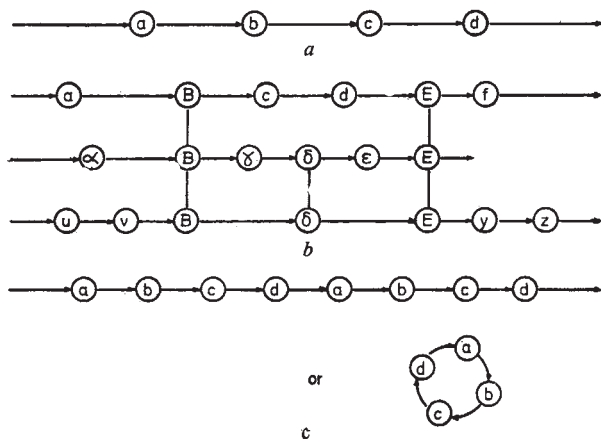


Fig. 1 a, Episodic time; b, an episodic time scale; c, cyclic sequences.

the less complex concept, while at the same time adding to it. We shall be particularly concerned with patterns that eventually repeat themselves in time, although the sociology of time need not be confined to such regularities.

Episodic Time

At its most fundamental, time implies little more than the notions of "before" and "after"—of one event following another irreversibly. Whether or not these events are linked causally, the chain may only be traversed in one direction. Consciousness implies memory, and with memory previous successions of events may be reviewed in retrospect, and the sequence of future events to some extent anticipated. This way of representing time we call *episodic* (Fig. 1a); mathematically speaking, time is merely the relation defining the ordering of a set of discrete *episodes* or *events*.

An individual may, for example, remember a series of climatic events, such as a drought, a cyclone, or a freeze-up; a series of births, marriages and deaths in the Royal House (such as "In the year that King Uzziah died . . ."); or a series of events in his own personal life. Although the events in each series may follow one another in correct chronological order, the important events are likely to be drawn out, and the less important compressed or eliminated (as in compiling a history of almost anything), almost without respect to their actual duration. Episodic time thus has no quantitative measure, and can seem to be purely subjective.

Nevertheless, by correlating such individual sequences, an objective episodic time scale can be established for a whole society. One of the methods used to obtain information for census purposes about the age distribution in societies in which most people do not know how old they are is to ask them to recall what was happening in their own lives at various points of time simultaneous with events that can be dated from more general historical evidence⁵. By this device, the census takers are trying to quantify the general episodic time scale (Fig. 1b) which serves most people in the society well enough. Similarly, the cultural sequences of the archaeologist based on potsherds excavated from successive levels at various sites have only recently been dated absolutely by the radio carbon technique.

It is only a step from consciousness that events occur in sequence to noticing that many such sequences repeat themselves. It is difficult now to disentangle a purely episodic view of time from this cyclic characteristic, a *cycle* being defined as a sequence which is repeated (Fig. 1c). The notion that *all* time sequences are essentially cyclic is widely held. This attitude seems to be deeply entrenched in primitive societies, where no doubt the cycle of the seasons matters more than in modern societies: this may be one of the reasons for the neglect of the whole subject by most social scientists in such societies; Goody⁵ and Leach being two of the exceptions.

Leach has described the primitive attitude to time. "Time can be regarded as a recurring cycle. Certain events repeat themselves in definite sequence. This sequence is a continuity without beginning or end, and thus without any clear distinction between past and present. The most important time-sequences are seasonal activities and the passage of human life. Both these cycles are conceived as of the same kind."⁷ Eliade, speaking more of ancient societies, says that archaic man "acknowledges no act which has not been previously posited and lived by someone else, some other being who was not a man. What he does has been done before. His life is the ceaseless repetition of gestures initiated by others."⁸

The quotation from Leach raises a question about the "passage of human life". In ordinary language we refer to a "life cycle": is this usage consistent with our present definition? A particular human life, as it progresses through various stages in its biological, psychological and social dimensions, is certainly a sequence of events (Fig. 2a). But these events are unique to the person who lives them. The individual cannot repeat his whole life pattern, from birth to death, in the same way, say, that he repeats himself in one respect by going to sleep on each ordinary night. Nevertheless, it is useful to retain the word "cycle" in this context, without an attendant adjective to distinguish a sequence of behaviour repeated by the *same* individual from an identical sequence repeated by *another* individual. The common usage of the term "life cycle" is justified if one does not think of it from the point of view of an individual as he sees himself, but rather as he sees others (including himself) as a member of a society or species. Everyone is in some degree repeating the sequences of behaviour of other people who have preceded him, doing the same kinds of things at the same age, always doing what others have done before. This is a characteristic of biological systems with almost no analogy in the world of physics.

It is convenient, on the other hand, to distinguish a relatively complete cycle, repeating as a closed loop, from a mere *recurrence* (Fig. 2b), or repetition of some characteristic type of event in otherwise different circumstances. An eclipse, or the return of a comet, a cyclic phenomenon astronomically, is seen by most men as a historically recurrent event, scarcely to be distinguished in principle from the occasional eruptions of a volcano or one of the military campaigns that has ravaged Flanders over the centuries. It is true that the recurrence of a particular event may imply its repetition in a sequence containing several other events with which it is correlated or causally connected. Each eruption, for example, would be followed by the flight of the population, the sporadic return of refugees, the rebuilding of houses, the restocking of farms and the eventual return to normal life. Such sequences of social or psychological behaviour are obviously of great interest as patterns in time, but we should prefer not to use such phrases as "the cycle of resettlement" to describe them. We want to say, "History repeats itself, but is not cyclic."

Time as a Continuous Variable

At the next level of sophistication, time becomes a numerical variable. The interval between notable episodes, such as the death of two successive kings, is given a measure by counting

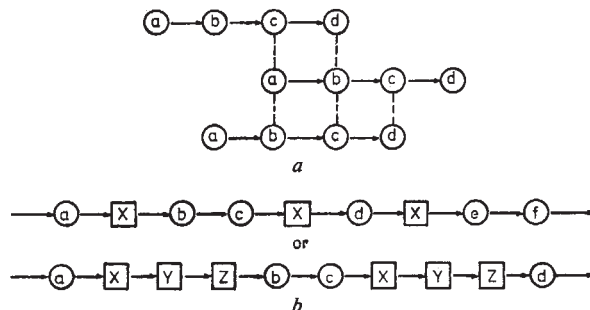


Fig. 2 a, Life cycles; b, recurrences.

regular astronomical events like the passing of the seasons, or full Moons, or days (Fig. 3a). This interpolation is done with greater or less accuracy in all but the most primitive societies, so that any event or sequence of events can be assigned an epoch or a duration. Less precise schemes of counting have gradually given way to more precise, as the years have become ordered into a series starting from zero, say, at the supposed foundation of Rome, or at the birth of Christ, as the days are assigned their places in an annual calendar, and as each day is divided into hours, minutes, seconds, milliseconds, microseconds, nanoseconds, by successive refinements of the clock—a device which Mumford⁹ saw outranking the steam engine as the key machine of the modern industrial age.

Clock time thus becomes, by successive subdivision, a continuous variable, analogous to the length coordinate along a line in space (Fig. 3b). It is the one dimension of material existence that is both universal and quantified. Ignoring the subtleties of relativity theory, which are irrelevant to human activities on the earthly scale, we can properly assign to any event an exact number—at 27 seconds past 18 minutes past 7 p.m. on the 31st day of October in the year 1970 Clare Ziman began her piano practice, and at 10 seconds past 10 minutes past 8 p.m. on the same day Sophie Young began hers—from which can be computed the exact duration of any particular sequence in which we are interested—a lesson, a task, a journey, a marriage, or a life.

It is not our present purpose to discuss the physics or metaphysics of the measurement of time. The important fact is that human behaviour, individual or social, is to some extent governed by biophysical processes which have their characteristic rates on the clock time scale, and cannot therefore be described completely in the language of episodic time. Many phenomena, for example, may be assigned their typical *relaxation times*—the average time for an effect to fade away (Fig. 3c). Thus, a fit of temper may have a relaxation time of a few minutes, the satiation of hunger by a meal lasts for a few hours, a week is said to be a long time in politics, while great political revolutions have consequences over a century or more. Notice that these statements imply recurrences of similar events for comparison, but carry no implications of periodicity.

Another typical time measurement would be the *mean free time* between recurrences of some characteristic event—for example, between changes of job or between strikes (Fig. 4a). This may be, in itself, a meaningful psychological or social parameter—at one factory, say, the mean free time between strikes might be twice that at another—without being directly related to a particular relaxation effect or referring to a strictly cyclic phenomenon.

The adaptation of our definition of cyclic behaviour to clock time is not unambiguous. It is necessary to introduce a term such as *periodic* to refer to any event or sequence of events that recurs at regular intervals—typically, Christmas, that comes but once a year, or breakfast, that recurs within a *period* of 24 hours $\pm$ 10 minutes in any well-ordered household (Fig. 4b). The calendar of the saints days, or the daily round of domestic life, can then be called a *periodic cycle*. In any case it will be as well to follow the convention of physics and regard the *frequency* as the reciprocal of the period, that is, the number of

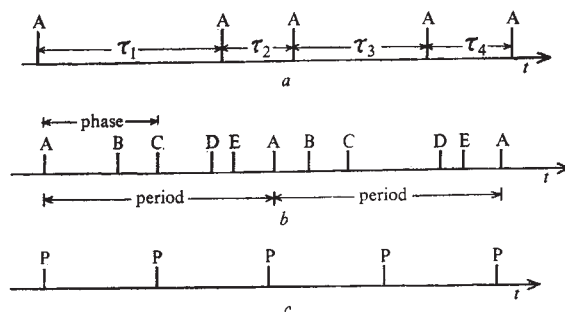


Fig. 4 a, Mean free time: $\bar{\tau} = \frac{1}{n}(\tau_1 + \tau_2 + \dots + \tau_n)$; b, a periodic cycle; c, a periodic recurrence, or pulsation.

recurrences of a periodic event or cycle in a longer interval—for example, Quarter Days occur with a frequency of four per year.

In considering a genuine periodic cycle, it is natural to close up the ends of the "circle", and to view time as flowing continuously from one event to the next without a break. Where this is done it becomes necessary to adopt a convention for marking a beginning to each repeated period by reference to one or other of the events in the sequence. Calendar years, for example, begin at 0001 h on January 1. The relative position in time of some other event in the cycle would then be the *phase* of that other event—for example, the various phases in the cycle of the Moon.

These definitions obviously merge into one another. The intervals between recurrences of some sudden, sharp event may become so nearly equal that we should cease to think in terms of mean free times and begin to talk of periods. In such cases, we could perhaps regard the time behaviour as *pulsating*—the nearly regular repetition of a well-defined event in the manner of the pressure of the blood in the body (Fig. 4c). On the other hand, we should still recognize some cycles as essentially periodic, even when they do not repeat at precisely equal intervals. On a camping holiday, for example, meal times tend to wander, while still preserving the essential pattern of the domestic cycle dominated by work and school: in the absence of strong clock cues, the basic relaxation mechanism of our digestive system would still encourage us to keep the cycle fairly regular.

Phenomena dependent on Time

The next stage in precision is to measure not only time in numbers but also the "events" which are related in time, such as changes in the price of food, or the level of wages, the numbers of unemployed, or the number of members of parliament commanded by a particular party (Fig. 5a). One can then observe whether some quantity depends on time. If such a number varies irregularly with time we should call it a *fluctuating* function of time; if it varies regularly then it can properly be termed *oscillating* (Fig. 5b). A cyclic movement of a measurable quantity up and down would thus be defined as an *oscillation*. Such cycles are, of course, of paramount importance in physics.

Within the social sciences, this approach is less typical of sociology than of economics, where money is a common measure of the value or price of different goods and services, which would be almost as precise in its way as the measure of time itself if it were not for continuous changes in price. Trade cycles or stock exchange cycles are patterns that can emerge from such a scrutiny. The behaviour with which sociology is chiefly concerned—demography apart—does not lend itself so readily to such an approach. But this does not mean, of course, that cycles, pulsations, and other time-dependent phenomena cannot be detected. One can decide on the basis of observation whether a series of events that precede, or follow, say, the annual budget, are sufficiently similar over a period of years to justify speaking of cyclic phenomena, even though one cannot represent these observations as mathe-

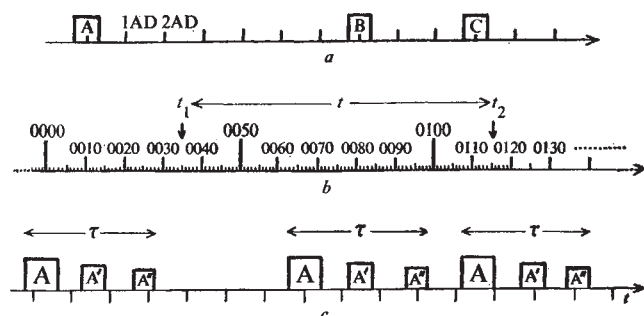


Fig. 3 a, Measured time; b, clock time; c, a relaxation time.

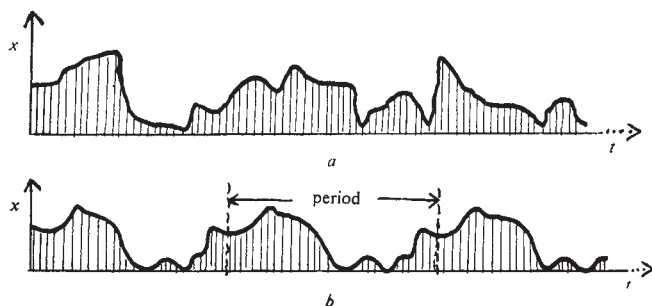


Fig. 5 *a*, A fluctuating function of time; *b*, an oscillating function of time.

mathematical functions. The behaviour of civil servants or government ministers is amenable to observation, description, and comparison, even though only the time dimension can be expressed in numerical terms. If there is any novelty in our present approach, it is in stressing the significance of this sort of analysis, which makes full use of the quantitative character of time itself without attempting to bend the time-dependent observables to a numerical representation.

Levels of Cyclic Behaviour

So far we have been discussing time-dependent phenomena at three levels of formal mathematical sophistication. We now consider cyclic behaviour at three different levels of social organization in order of increasing complexity. The three levels are those of the individual, of the small group, and of a society as a whole. Since people operate at all levels simultaneously, the subdivision is no more than a convenient simplification for our present purposes.

Cycles of personal behaviour or *routines* (which, we suggest, could be used as an alternative word for cycles that appertain to the behaviour of an individual), are partly governed by endogenous biological mechanisms which need to be sustained by food and sleep at more or less regular intervals. These endogenous cycles are, in their turn, geared fairly tightly to exogenous astronomical cycles. Such *circadian* cycles—to use the biological term for cycles with a period of about 24 hours—provide the framework within which the individual can establish his own routines for times of rising, eating his meals, travelling to and from work, working, shopping, watching television, gardening, or whatever it may be. The degree to which people arrange their lives in a cyclical pattern varies from person to person; the amount and correlates of variation is one of the topics which require investigation. But clearly almost everyone does adopt a series of routines, partly to save himself from having to decide afresh each day how to organize his time and partly in the interest of cooperation with others. People can become so conditioned to their routines that these become habits which are hard, indeed uncomfortable, to break. A feature of modern society, in which astronomical events are not all-important, is that the individual may become so conscious of clock time that he even regulates his private behaviour to strict periodicity—always going to bed at 11.15 p.m., say, whether he is sleepy or not.

By his existence in society, the individual is geared to many more routines than the circadian. There are weekly cycles—each Monday may have its peculiarities which make it different from Tuesday, and Saturday in any one week may be much more like Saturday in another than it is like any Friday. Even in an industrial society, there may be monthly cycles, related, for example, to the dates on which salaries (as distinct from wages) are paid and mortgage interest remitted; and there are many annual cycles tied in with the seasons and the influences they exert over work and leisure, as well as all the changes implicit in the life cycle itself. For most people there are also many other more idiosyncratic cycles, to do with their work or their family life, which are not so closely related to the standard periodicities of the calendar.

The point we are making is that at any given moment a person is locked into several different cycles with different periods, and his behaviour from moment to moment is the resultant of influences drawn from all the different cycles, in a manner reminiscent of Fourier's theorem in physics. On a particular Friday afternoon in November 1970, a senior civil servant at the Treasury, who has just had his monthly salary paid into his bank, may be hurrying to finish the work he is doing on some departmental estimates, which are at a particular position in the pipeline leading to the annual budget, so that he can get away before the rush hour to drive down to the country to spend the half-term weekend with his daughter. Perhaps he does not mind "getting behind" as much as he used to because he is not so far from retirement and has got as high in the civil service hierarchy as he is ever likely to. A constant problem for him, as for anyone else with some freedom in the allocation of his time, is to decide the relative priorities of action in cycles that do not neatly mesh—particularly the priority of long-period cycles over shorter ones. This means, of course, that Fourier's theorem is not strictly applicable, since the various cycles are not additive in any arithmetical sense; the "behavioural resultant" often reflects the strongest influence at the moment and is not an averaged response to them all.

The final relationship of all the cycles, with their different periods, all operating simultaneously, we call a *rhythm*. Although this is a musical term, without significance in physics, it is much used in biology, and carries many suggestive analogies. The aesthetic appeal of musical rhythm is not necessarily the same as the satisfaction to be obtained from a complex pattern of routines with periods of hours, days or years. The psychology of this whole subject, including attitudes to "punctuality", is of at least as much interest as its sociology. In this context the word, rhythm, is intended to be value-neutral, without specially favourable connotations.

Small Group Interaction

The example of the civil servant illustrates the interaction of individuals within a group as well as the interactions between the various cycles in a personal routine. Membership of a small group, just as much as of a large one, means that individual cycles need to be *synchronized* or *harmonized* (Fig. 6)—brought into agreement, changed in phase or period, so that significant events may always occur simultaneously. In other words, the *periods* of the routines of the two individuals must be made equal, or else must stand in some simple integral ("harmonic") ratio.

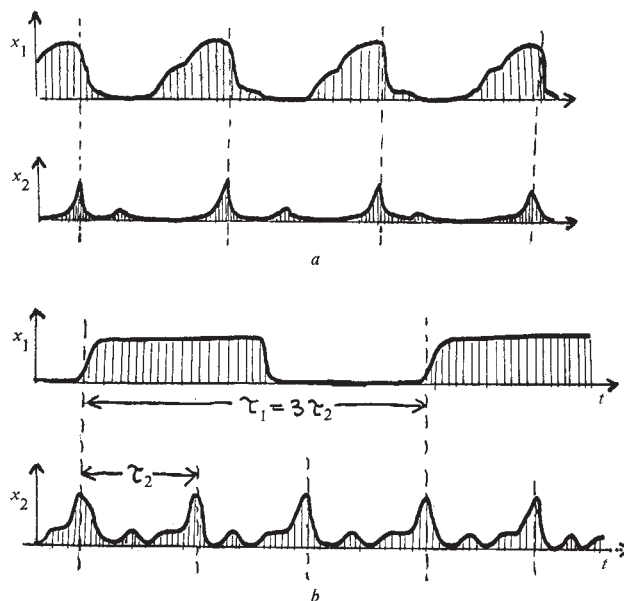


Fig. 6 *a*, Synchronized cycles; *b*, harmonized cycles.

This can be achieved in various ways, of which the commonest is to subordinate a *dependent* cycle to a *dominant* one (the latter controlling the former). Typically, this occurs by the *entrainment* of a cycle of variable period to the more precise period of the dominant routine. Thus, a school-child may be required to get up to have his breakfast with his father, and to take about as long over it, the whole being determined by the father's need to catch a particular bus to work. The work cycle entrains the getting up cycle of the father, which does the same, in turn, for that of the child. With very young children the relationship is inverted; their digestive cycles entrain the domestic cycles of the parents. Dominance is, however, seldom complete. Each individual's routine acts back on and changes the timing of the others, just as two physical pendulums change each other's frequency when coupled together.

As individuals and small groups are built into more complex social organizations, their cyclic behaviour patterns combine into a *system*—an assembly of many interacting cycles—which has its own characteristic time-like properties. In such a system, multiple synchronization, so as to keep a particular phase of one cycle strictly in step with a particular phase of another, becomes essential (Fig. 7).

A school is an example of a relatively simple system. The caretaker, who had to clean the school the evening before, has to open the school gates at 8.15 a.m. The children arrive between 8.30 and 9 (some brought by parents who have gone through standard and carefully timed sequences in order to be punctual at school). The head teacher arrives at 8.40, the teachers from 8.45 on, the van from the school meals service at 11.30 with the containers of dinners cooked the night before, the cook at 11.30, the dinner-ladies from 11.45. Each teacher and each batch of children have to make their appearances in the right points in space at the right points in time and to scatter and re-assemble in the right conjunctions or the whole organization will cease to hold together. We are regarding the interconnected cycles as synchronized although they do not necessarily start and end at the same time or have the same period. The caretaker has to begin work before the teachers and the teachers may have to continue with their marking and preparation after the children have left the premises. The engagement of one cycle after another into the assembly in the correct order at the correct time is vital to the coherence of the whole. *Antecedent* cycles (which precede others in their starting times) can be distinguished from *postcedent* cycles.

A school is, as we said, an example of a relatively simple system. It belongs to the larger system of the local education authority which lays down rules for the starting and finishing times of days, weeks and terms; the dates when new staff have to be advertised for, interviewed and take up their appointments; the dates by which requests for additional capital expenditure have to be put up to the office ready for particular meetings first of the education committee, then of

the finance committee, then of the whole council; and hundreds of other matters besides. The operations of the authority are as much timetabled as the school. As the school has to fit into the timetable of the authority, so does the authority have to fit into the timetable of the Department of Education and Science as far as approvals for capital expenditure are concerned. The DES in its turn is bound by the general timetables of the government, including, above all, those of the Chancellor of the Exchequer and his advisers. Chinese boxes are not the right analogy, for all the sub-systems which go to make up, say, the educational system, which goes to make up the society, are composed of moving parts, the cycles to which we have been drawing attention in this paper. An orchestra or a corps de ballet is a more apt analogy, with GMT and the calendar as the conductor's beats.

People and Cycles

We are not claiming that the individual, unless perhaps he is employed in a mass production factory, ordinarily sees his life in the way we have presented it; he might find it "boring" if he did. He observes rather the deviations from the rule, the differences which, in the nature of time, make each "repetition" unique. The message is evidently carried (as in radio) by the *modulation*, or variations from regularity, in the cycles of his perennial existence. But whether they see it in this light or not, people are caught up in innumerable, interlocking cycles at the level of the individual, the small group and the system. In the background is the music of the spheres: the astronomical cycles partially entrain the biological cycles and the biological forces entrain or stimulate individual routines. Society builds on this propensity. Although social behaviour, outside a range of occupations to do with the land and the sea, is not directly subject to astronomical forces, it is convenient to use them symbolically to orchestrate the ensemble, even in an industrial society. The actors learn by repetition to become more proficient in their parts. The regularity of cycles that are taken for granted allows a collective endeavour which would be impossible if the whole interlocking series of systems had to be devised deliberately in every particular instead of only in some.

This, then, is the picture—but only in the most general outline. It will become more differentiated and exact only as study proceeds, not only of the various sorts of cycles in behaviour, of the rituals which are embodied in them, of the information feed-back cycles which help to maintain synchronization, and of the psychological and biological mechanisms underlying the social routines, but also of the variations in the extent to which behaviour is cyclical at all, between one person and another, one group and another, one class and another and one institution and another. Nor should non-cyclical behaviour patterns be neglected, as typified by relaxation phenomena at the individual and social level. The social sciences will have to take a look at their stock in trade—human behaviour—in its time dimension.

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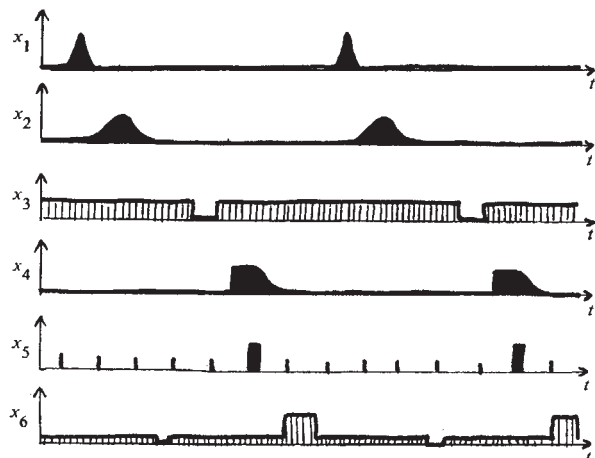


Fig. 7 A system of cycles.

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1-10 keV X-ray Sky near the Galactic Centre

by
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A series of rocket experiments has provided insight into the nature of the X-ray sources near the galactic centre.

THE region of the galactic centre is known to have numerous X-ray sources in the energy region 1–10 keV (refs. 1–12). During the period 1967–1969 we have carried out four experiments^{9–12} on three sounding rocket payloads to resolve source confusion in this region and to measure source positions with good precision. We have also carried out spectral and angular size measurements^{13–15} during these flights. It is now possible for us to describe the overall appearance of the X-ray sky in this celestial region. Although no optical or radio identifications of these sources have been made, these results eliminate various hypotheses concerning possible types of optical and radio counterparts. The source distribution in galactic coordinates also provides information about the source distances. Furthermore, the source positions reported here

make possible future observations which require prior knowledge of source locations.

The first of the four experiments (hereafter designated I) took place on July 7, 1967, and located the positions of six sources (GX3+1, GX5–1, GX9+1, GX9+9, GX13+1, GX17+2) in the region $3^\circ < l^\text{II} < 17^\circ$ with uncertainties of $\sim 1/4^\circ$ (ref. 9). The second experiment (II) on July 26, 1968, refined these positions and reduced significantly the ambiguous situation at $340^\circ < l^\text{II} < 350^\circ$ (ref. 10). The third experiment¹¹ (III) on October 2, 1969, made use of the rotating modulation collimator to measure the positions of GX3+1, GX5–1, GX9+1 and GX17+2 with precisions of $1'$ to $3'$. The fourth experiment¹² (IV) made use of a slat collimator which was carried on the same rocket flight as III. When the data of IV are combined with those of II, the positions of four new sources are obtained with precisions of $\sim 1/4^\circ$. The data of IV, so far unpublished, are presented in the last section of this article.

Summary of the Results

The cumulative results of the four experiments are presented in Fig. 1 and Table 1. The conclusions which we can draw are:

Table 1 X-ray Sources near the Galactic Centre

Source	Experiment *	l^II	Coordinates b^II	$\alpha(1950)$	$\delta(1950)$	Error limits †	Angular size ‡	Observed intensity §	Other designations //
GX340+6	II, IV	339.62°	+6.20°	16 ^h 17.1 ^m	–41°12'	20'	—	1.0	SIA, L4
GX340+0	II, IV	340.06	+0.05	16 ^h 43.4 ^m	–45°05'	17'	—	1.0	Sco XR-4 SIB, L2-L3, W340-2, Ara XR-1
GX342-8	II, IV	342.50	–7.88	17 ^h 28.8 ^m	–47°53'	14'	—	0.9	S2, W341-6, Ara XR-1
GX349+2	II, IV	349.21	+2.39	17 ^h 04.1 ^m	–36°29'	17'	<2.0'	1.0	S4, GX-10.7, L6, Sco XR-2
GX358-8	II, IV	357.77	–8.23	18 ^h 10.9 ^m	–34°57'	35'	—	0.3	S6, GX-2.5, Sco XR-6
GX3+1	I-IV	2.291	+0.792	17 ^h 44 ^m 49 ^s	–26°33.0'	1.7'	<1.5'	0.4	GX+2.6, L14, Sgr XR-1
GX5-1	I-IV	5.079	–1.020	17 ^h 58 ^m 04 ^s	–25°04.7'	1.2'	<1.5'	1.5	GX+5.2, L17
GX9+9	I, II, IV	8.49	+8.99	17 ^h 29.0 ^m	–16°58'	12'	—	0.4	—
GX9+1	I-IV	9.082	+1.152	17 ^h 58 ^m 35 ^s	–20°31.5'	1.7'	<1.5'	0.9	GX+9.1, L18
GX13+1	I, II, IV	13.52	+0.47	18 ^h 10.3 ^m	–17°00'	15'	—	0.3	L19, Sgr XR-3 GX+13.5, L20
GX17+2	I-IV	16.435	+1.282	18 ^h 13 ^m 10 ^s	–14°03.0'	2.6'	<2.0'	1.0	Sgr XR-2 GX+16.7, L21 Ser XR-2

* Experiment I, July 7, 1967 (ref. 9); II, July 26, 1968 (ref. 10); III, October 2, 1969 (ref. 11); IV, October 2, 1969 (ref. 12).

† Radius of error circle. The probability that a source lies within the limits is about 90%.

‡ From ref. 13; also modulation collimator data from experiment III (ref. 11).

§ Weighted average of the experiments in units of 10^{-8} erg cm^{-2} s^{-1} (1.5–8 keV).

// See caption to Fig. 3 for references.

(1) At least eleven discrete X-ray sources lie between galactic latitudes -10° and $+10^\circ$ in the region $335^\circ < l^\text{II} < 20^\circ$. The data also indicate the existence of other, less intense, unresolved sources in this region.

(2) There is no correlation between the positions of these X-ray sources and the positions of the following catalogued optical, infrared, and radio objects: bright nebulae¹⁶, galactic novae¹⁷, magnetic stars¹⁸, planetary nebulae¹⁹, Wolf-Rayet stars²⁰⁻²¹, 2.2 μm sources (unpublished report by Neugebauer and Leighton), HII regions²²⁻²⁴, OH emission sources (unpublished report by Ball and ref. 25), pulsars (using Terzian's updated list of November 11, 1970), and supernova remnants²⁶. None of these objects overlaps an X-ray error box with the exception of an HII region near GX340+0 (ref. 24). The latter is most likely an accidental coincidence because of the high density of HII regions near the galactic equator. We have obtained upper limits for X-radiation from the galactic centre ($I_x < 2 \times 10^{-9} \text{ erg cm}^{-2} \text{ s}^{-1}$), from W24 which exhibits numerous molecular radio emission lines²⁷ ($I_x < 2 \times 10^{-9} \text{ erg cm}^{-2} \text{ s}^{-1}$), and from the supernova remnants SN1604 ($I_x < 0.6 \times 10^{-9} \text{ erg cm}^{-2} \text{ s}^{-1}$) and W28 ($I_x < 1.5 \times 10^{-9} \text{ erg cm}^{-2} \text{ s}^{-1}$).

We note that our error limits effectively rule out several proposed candidates for the X-ray sources, such as optical HII regions²⁸, Wolf-Rayet stars²⁹, a supernova remnant (for GX5-1) (ref. 30), and a variable, ultraviolet star with intense emission lines (for GX3+1) (ref. 31). We also note that an optical search to $B=17$ (ref. 32) and a radio search at 4.6 cm to about 0.05 f.u. of the precise $1'-3'$ positions yielded no candidates for the X-ray sources³³ (1 f.u. = $10^{-26} \text{ W m}^{-2} \text{ Hz}^{-1}$).

(3) The galactic latitude distribution of the sources is characterized by seven sources which lie quite close to the galactic plane ($|b^\text{II}| \lesssim 2^\circ$). If they lie in the galactic disk randomly distributed within 100 pc of the plane, they are probably at least 3 kpc from the Sun. This is consistent

with the low energy spectral cutoffs observed for some of these sources^{14,15,34}, which correspond to about 2×10^{22} H atoms cm^{-2} between them and the Sun. On the other hand, we note that the other four sources are at ($|b^\text{II}| > 6^\circ$). These are probably significantly closer to the Sun.

(4) Variations in intensity exceeding a factor of two are excluded by our data for the sources which we report over the 1 to 2 year periods of our observations. We also find our intensities to be roughly comparable to those reported by other groups. This places them in a category different from that of the nova type X-ray sources Cen XR-2 (refs. 35 and 36) and Cen XR-4 (ref. 37) which flare up and then decay with time constants of about one month. There is some evidence in our data for variations of 20 to 40%, but we cannot exclude systematic errors of this magnitude. Also, as we shall see later, the early (1964) results² of the AS & E-MIT group from a spinning rocket yielded a bright source, Sco X-2, at a position sufficiently removed from those reported herein, so that there exists the possibility of a significant variation in intensity. We also note the early report of variations by the NRL group⁶. All in all, the sources in the region seem to be stable by comparison with the nova-like sources, however.

(5) The photon number spectra of these sources fall rapidly in this energy region (1-10 keV) with spectral indices of -1.3 to -2.2 (ref. 14). Because of the narrow bandwidth of the measurements they can also be fitted with exponential thermal bremsstrahlung spectra with temperatures of the order of 5 keV (refs. 14 and 34). Spectral data above 20 keV would yield more information. Results from balloon experiments indicate that some of these sources have a hard component comparable to that of the Crab Nebula³⁸⁻⁴⁰.

(6) The sources are typically small ($< 2'$) in angular size¹³ and typically show no significant radio flux³³ (see section (2) above). Thus these sources probably are not supernova remnants of the kind now known, but are more typical of

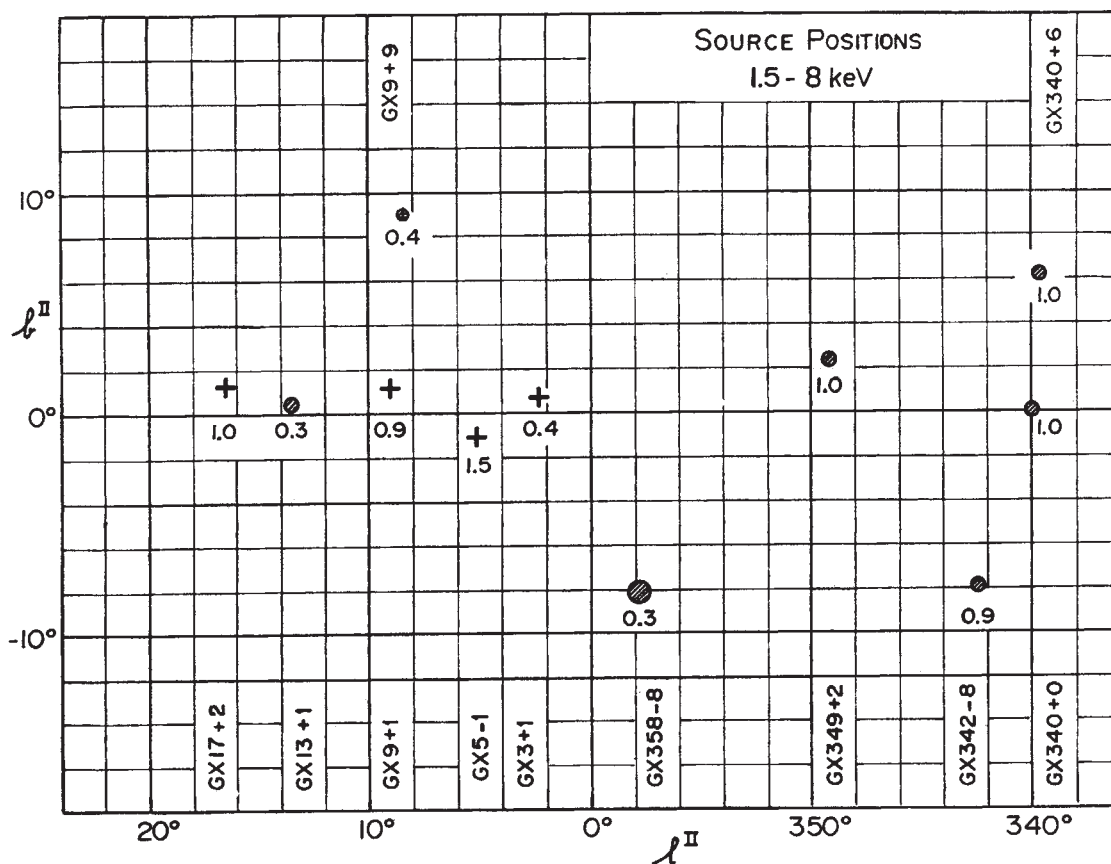


Fig. 1 Summary map of X-ray sources. The circles represent the error boxes defined in Table 1. The crosses indicate positions which are known with a precision of $1'$ to $3'$. The numbers by each source represent its intensity in units of $10^{-8} \text{ erg cm}^{-2} \text{ s}^{-1}$ (1.5-8 keV).

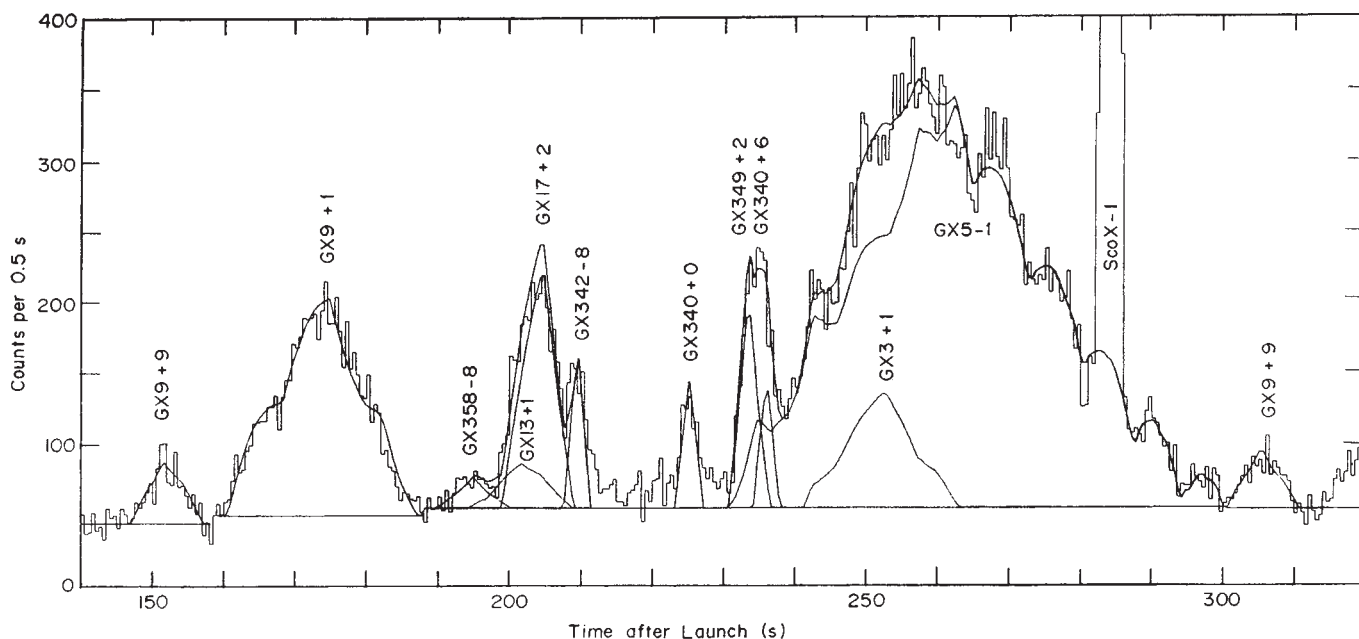


Fig. 2 Histogram of counting rate versus time for the rotating slat collimator (Experiment IV). The lines represent the expected response for the "best fit" source positions and intensities. In a multiple-source region, the outer curve gives the sum of the responses. The complex structure in GX5-1 arises from a leaking control jet (roll axis) and the abrupt jet firings which overcome its effect.

Sco X-1. This latter possibility has not been excluded by optical searches of the 1° - 3° X-ray error boxes which unfortunately lie in moderately obscured regions³².

Experiment IV

The most recent experiment was a scan by a slat collimator ($1.1^{\circ} \times 60^{\circ}$ FWHM) carried aboard the payload which also included the "rotating" modulation collimator. The slow rotation ($1.2^{\circ} \text{ s}^{-1}$) of the payload about the view (pitch) axis caused the field of view of the slat collimator to rotate about its centre. The centre of rotation wandered $\sim 1/2^{\circ}$ on the sky during the 200° rotation, but was positioned approximately at $l^{\text{II}} = +6.7^{\circ}$, $b^{\text{II}} = -2.0^{\circ}$. In a rotary scan, the time which a source spends in the field of view is approximately inversely proportional to its distance from the centre of rotation. Thus the rotating slat collimator can give two dimensional (radial and azimuthal) source positions. The radial position errors are typically greater than the azimuthal errors, however.

The X-ray detectors were two proportional counters with 50 μm Be windows and a gas filling of 4.7 mg cm^{-2} argon plus 1.7 mg cm^{-2} xenon. The data presented here correspond to the energy interval 1.5 to 8 keV. The total effective area of the detection system was 200 cm^2 . The flight took place from White Sands Missile Range on October 2, 1969, at 20 h 05 m sidereal time.

Fig. 2 presents the counting rate data from this experiment. Each apparent source or source complex was studied by means of at least chi-square analysis. The smooth curves represent the "best fit" solution that we have obtained. We included only sources clearly required by the χ^2 analysis. Furthermore, the least convincing sources (GX13+1 and GX340+6) were known to exist from earlier data (Fig. 3). The data of Fig. 2 can be understood qualitatively by a comparison with Fig. 3, which shows the centre of rotation and the X-ray source positions.

The collimator aspect was obtained from stellar photography by the two cameras used for III (ref. 11). Inflight calibration on Sco X-1 (a blue starlike object) and GX9+1 (position obtained from III) was precise to $\sim 2'$. This calibration was reconfirmed in that the analysis extracted lines of positions for GX3+1, GX5-1 and GX17+2 which lie less than $4'$ from the $1'$ to $3'$ positions obtained from III.

The apparent increase in background in the region between

the transits of GX17+2 and GX349+2 could be due to weak or more distant sources which lie near the galactic plane. The long field of view of the collimator is roughly parallel to the galactic equator during this period. We find that such effects do not modify the source positions which we report by more than a few arc minutes.

The source regions and lines of position defined by the χ^2 analysis are shown in Fig. 3. The six sources obtained from I at $3^{\circ} < l^{\text{II}} < 17^{\circ}$ were apparently all observed by this experiment. The high galactic latitude source GX9+9 was observed unambiguously for the first time since I. In the region $335^{\circ} < l^{\text{II}} < 350^{\circ}$, the results of II are shown as hatched areas. The intersections which we designate as sources (GX340+0, GX340+6, GX342-8, and GX349+2) are the only ones which are easily compatible with the data of II and IV. These intersections all lie within 2° or less of the most probable positions obtained from II. The combined data of II and IV are consistent with only a weak source at the location of Sco X-2 and W344+3. The latter sources were observed from spinning rockets in 1964 and 1968. We further note that the data peak attributed to GX342-8 occurs when the collimator transits Ser XR-1 at $l^{\text{II}} = 36^{\circ}$ (refs. 6 and 7). Ser XR-1 was, however, reported as a weak source in 1967 (ref. 7) and in 1970 (private communication from Holt *et al.*) with an intensity less than $1/4$ of GX342-8.

We can now report the position of the source GX358-8 (Fig. 3) because of the weight of evidence from several flights. The AS & E source GX-2.5 (ref. 7) was shown to lie at $b^{\text{II}} < -5^{\circ}$ by I. The data from II showed a weak, but clear, data peak which yielded the line of position S6. The present data similarly yield the convincing peak labelled GX358-8 in Fig. 2. All three lines of position intersect as shown in Fig. 3.

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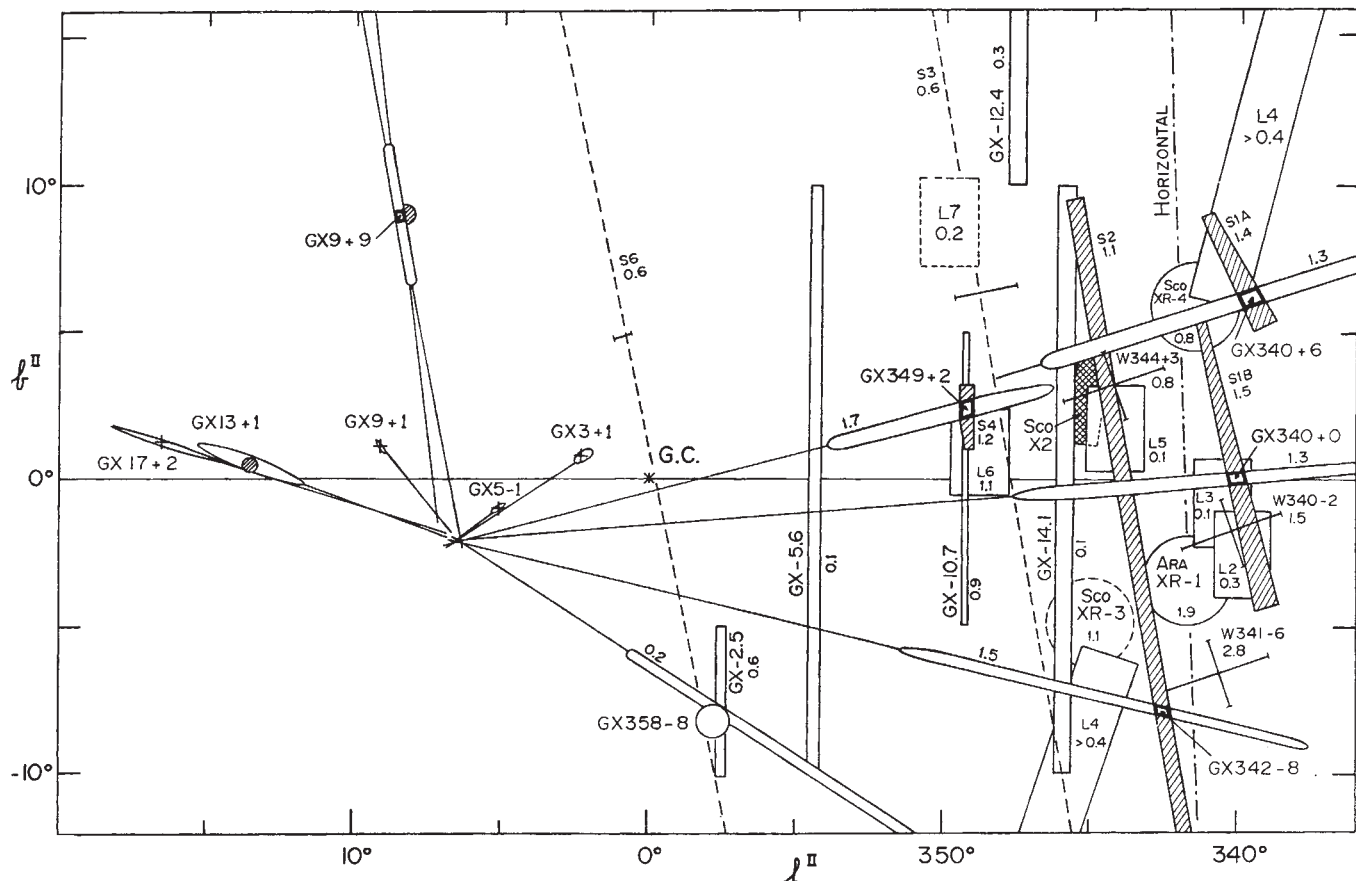


Fig. 3 Results from experiment IV. The centre of rotation, which wanders on the sky, is approximately at $b^{\text{II}} = -2.0^\circ$, $l^{\text{II}} \simeq -6.7^\circ$. The open ovals extending radially from this point represent the source error regions defined by this experiment. The intersections with the results of experiment II (hatched areas) define source positions. All results of previous experiments with errors of less than 2 deg^2 are given for $335^\circ < l^{\text{II}} < 350^\circ$. The two digit numbers indicate the reported intensities ($\text{counts/cm}^2 \text{ s}^{-1}$). The source designations indicate the experimental group: XR (ref. 6), X (ref. 2), L (ref. 5), GX $^{l^{\text{II}}}$ (ref. 7), S (ref. 10), W (ref. 8), GX $^{l^{\text{II}}b^{\text{II}}}$ (refs. 9–11).

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Thermodynamics, Chemical Reactions and Molecular Biology

by

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An extended statement of chemical equilibrium calls for consideration of the integral $\int_0^T \Delta C_p dT$, in addition to $T \int_0^T \frac{\Delta C_p}{T} dT (= T\Delta S_T^0)$ and ΔH_T^0 —the classical terms of the equation $-RT \ln K = \Delta H_T^0 - T\Delta S_T^0$. The integral $\int_0^T \Delta C_p dT$ is not negligible for macromolecules and particularly biopolymers, and its direct experimental determination at all temperatures down to 0 K is therefore indispensable for thermodynamic understanding of the objects of molecular biology.

sensical quantities in a new equation. Thus the question arises whether or not the choice of ΔH_T^0 and $T\Delta S_T^0$ is the only meaningful one and, if not, whether it is the best choice that could have been made.

Thermodynamic Concepts

Early in the development of chemical thermodynamics ΔH_T^0 was chosen (and $T\Delta S_T^0$ followed inevitably from the definition of entropy $dS = dq/dT$). (Even earlier the conceptual uniqueness of ΔH_T^0 had been overrated in Berthelot's view of the work obtainable from chemical reactions.) Although ΔH_T^0 is certainly the logical choice for a direct thermodynamic measurement with chemical reactions, the ease and precision of such measurements do not necessarily mean that ΔH_T^0 is also the best choice for a fundamental statement such as equation (1). Suitable criteria must be adopted to investigate other possibilities from a viewpoint of conceptual clarity and power. When chemical thermodynamics is used for commonsense purposes and extended by molecular interpretations beyond purist formalism, it is supposed to describe the transformations of energy which are inseparably linked with transformations of matter. Our criteria will therefore be the direct relations of the thermodynamic quantities selected, to the formation or breaking of chemical bonds between atoms, the only processes by which chemical product matter can be formed from chemical reactant matter.

The laws of chemical equilibrium are conventionally determined (see Max Planck¹, page 287) in terms of the heat of reaction term ΔH_T^0 and the Clausius entropy term $T\Delta S_T^0$. Indeed, these two quantities provide the thermodynamic foundations of the chemical and life sciences, and the statement

$$-RT \ln K = \Delta H_T^0 - T\Delta S_T^0 \quad (1)$$

is as infallible as the laws of thermodynamics. (Here $-RT \ln K$ is a numerical expression for collective or mass action, not individual thermodynamic properties of products and reactants.) Any number of equally infallible statements can, however, be obtained by simultaneously adding to or subtracting from the enthalpy and entropy terms in equation (1) some quantity—let it be called $\Delta \Gamma_T^0$:

$$-RT \ln K = (\Delta H_T^0 - \Delta \Gamma_T^0) - (T\Delta S_T^0 - \Delta \Gamma_T^0) \quad (2)$$

Although this simple operation does not affect the infallibility of equation (1) for thermodynamic accounting, it completely changes the physical interpretation of the two terms on the right hand side. Most of the possible choices for the magnitude of $\Delta \Gamma_T^0$ would no doubt produce physically non-

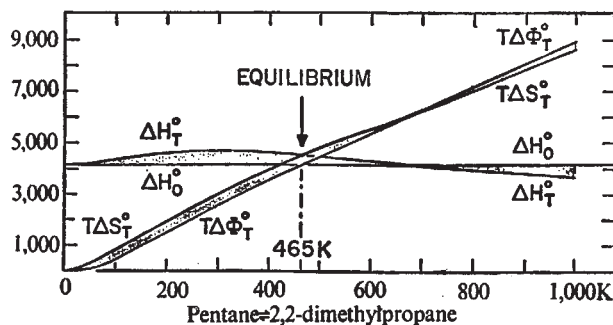


Fig. 1 Isomerization of a five carbon compound. Thermodynamic data from 0 K to 1,000 K, (a) in classical form (ΔH_T^0 and $T\Delta S_T^0$) and (b) in accordance with the free entropy concept by ΔH_T^0 and $T\Delta \Phi_T^0 = T \int_0^T \frac{\Delta C_p}{T} dT - \int_0^T \Delta C_p dT$. At the equilibrium point, 465 K, the difference between the two presentations is 10%.

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Two Contributions

It is difficult to show a direct relation between chemical bonding or bond breaking and the classical ΔH_T^0 and $T\Delta S_T^0$ terms. It can be shown that ΔH_T^0 is a composite, not a uniform quantity, and that the two contributions of which it is composed are of fundamentally different origin. They may be present in any conceivable known or unknown proportion and in the molecular view only one of the two contributions has a direct relation to chemical bonding.

Proof of this contention may be found by allowing reactants and products to be taken separately from temperature T down to 0 K or from 0 K up to T , while heat capacity differences ΔC_p are measured for every infinitesimal step to find the integral $\int_0^T \Delta C_p dT$.

Whenever this integral is not zero, an amount of heat $\int_0^T \Delta C_p dT$ must be liberated or absorbed during the reaction, in addition to other heat changes which arise from the formation or undoing of chemical bonds between atoms. In our low temperature experiment the reaction did not take place and the chemical bonds, which the reaction equation describes, were not formed. In these low-temperature experiments, we have, however, measured $\int_0^T \Delta C_p dT$, one contribution to the heat of reaction ΔH_T^0 . The other contribution obtained by subtraction, $\Delta H_T^0 - \int_0^T \Delta C_p dT$, is chemical bonding energy. It can be observed only when the reaction takes place, and even then it is in most cases obscured by the contribution $\int_0^T \Delta C_p dT$.

Integrals and Chemical Bonds

Because $\int_0^T \Delta C_p dT$ is obviously unrelated to the formation or breaking of chemical bonds between atoms, our concept² proposes that $\int_0^T \Delta C_p dT$ be subtracted out of equation (1) for a determination of the laws of chemical equilibrium, extended to cases where $\int_0^T \Delta C_p dT$ is finite or large.

One obtains from equation (2)

$$-RT \ln K = (\Delta H_T^0 - \int_0^T \Delta C_p dT) - (T\Delta S_T^0 - \int_0^T \Delta C_p dT)$$

This may be written

$$-RT \ln K = \Delta H_0^0 - \Delta W_T^0 \quad (3)$$

where

$$\Delta W_T^0 = [T \int_0^T \frac{\Delta C_p}{T} dT - \int_0^T \Delta C_p dT]$$

In equation (3) ΔH_0^0 represents the amount of heat (or, when the reaction is properly harnessed, energy of any kind: chemical, osmotic, mechanical, electrical or other), obtainable from the energy of formation of chemical bonds between atoms. At 0 K, ΔH_0^0 is defined as the heat of reaction; at other temperatures, ΔH_0^0 is a virtual quantity, invariant with temperature unless bond stretching as a result of thermal agitation leads to a slight reduction of the amount of work required to separate bond partners. (Such variations with temperature, if they exist, are subject to experimental proof by measurements of $\int_0^T \Delta C_p dT$ and ΔH_T^0 over the range under consideration. If the states concerned are inaccessible experimentally, they are reached in a mental process comparable with the concept of infinite dilution in solution theory.)

The term ΔW_T^0 of equation (3) represents work obtainable by conversion of "thermal" heat contained in chemical compounds and expendable in the performance of separating chemically bonded atoms in the compounds concerned. Equation (3) is consistent with the pertinent statement of statistical mechanics: $-RT \ln K = \Delta E_0 - RT \ln(Q_B/Q_A)$ regardless of the interpretation of the terms. The classical statement (1) presents a different view of the forces competing for chemical equilibrium.

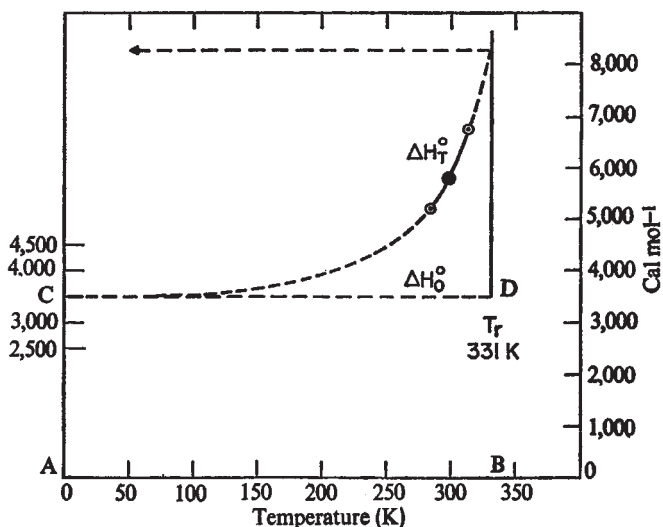


Fig. 2 Thermodynamics of unwinding the poly-A : poly-U double helix. Heats of reaction, one measured by Steiner and Kitzinger⁴ and three by Rawitscher *et al.*⁵, are plotted against the temperature axis AB. The plot is tentatively extrapolated

to $\Delta H_0^0 = (\Delta H_T^0 - \int_0^T \Delta C_p dT)$ with zero slope at 0 K (on third law considerations). This gives a tentative value for ΔH_0^0 (chemical bond energy for two hydrogen bonds per base pair) between 2,500 and 4,500 calorie mol⁻¹ or possibly less, compared with more than 8,000 measured as heat of reaction. (The curve cannot be sensibly extrapolated for zero slope at 0 K to 8,000 calorie mol⁻¹ (uppermost broken line), taking heat of reaction for chemical bond energy in classical manner (see Pauling⁷).

The plot represents $\Delta \Gamma_T = \int_0^T \Delta C_p dT$ with the temperature axis CD.

Our equation (3) uses for determination of the laws of chemical equilibrium two quantities with dimensions [calorie mol⁻¹]. No quantity with the dimensions of entropy [calorie mol⁻¹ K⁻¹] is involved and this may be considered a simplification.

Links with Planck

In an effort to relate the contents of equation (3) more closely to the classical statement (1) and, particularly, to one of three characteristic functions developed by Max Planck¹ (pages 120-122), we have previously² given the formulation

$$-RT \ln K = \Delta H_0^0 - T\Delta\Phi_T^0 \quad (4)$$

The term $T\Delta\Phi_T^0$ may be regarded as an entropy term, which is free and not bound and is not compensated in a simultaneous exchange of heat and entropy $\times T$ in equivalent amounts in the same direction between the reactant system and the surroundings, which would make the net change in free energy zero. Φ_T^0 represents standard "free entropy".

The symbol Φ was chosen because of the identity of our expression for free entropy with one of the three characteristic

functions already discussed which was designated Ψ , or Φ in earlier editions of Planck's treatise. Φ_T^0 is also identical with the free energy functions $((F-H_T^0)/T)$, tabulated in numerous standard works and textbooks. Planck's only important mention of chemical change in connexion with Ψ or Φ reads:

"The additive constant of integration still has to be considered. This could depend on p , and, besides, on the chemical composition of the system. The dependence on p is given by the first equation of (79b) by a measurement of the volume, V . The dependence on the chemical composition can be concluded from the measurement of such processes as are accompanied by chemical changes of state."

At that point Planck left the issue as it stood. At the time of his writing, the man made macromolecules of the modern chemist and the coded giant molecules of biological systems were of no concern to the physicist. The thermodynamics of most of the chemical reactions then known could be described satisfactorily with the terms of equation (1), as $\int_0^T \Delta C_p dT$ is often close to zero in these cases.

Near the end of the *Treatise*, however, Planck made a far-seeing statement and prediction, important to modern macromolecular chemistry and to molecular biology: "Accordingly, the determination of the laws of chemical equilibrium is made to depend on measurements of heat capacity and heat of reaction . . . to be sure, the experimental results available are not sufficiently extensive to test completely this far reaching conclusion from the theory".

In contrast to Planck's postulate the experimental determination of ΔH_T^0 and $T\Delta S_T^0$ in the classical equation (1) does not depend on measurements of heat capacity, either at room temperature or at any temperature between T and 0 K. Values of ΔH_T^0 and $T\Delta S_T^0$ follow simply from one measurement of heat and one chemical determination of K at room temperature, or even from two measurements of heat at room temperature without chemical analysis³.

If Planck was right in postulating that measurements of heat capacity are indispensable for a determination of the laws of chemical equilibrium, and if our extension of equation (1) into equation (4) has carried out Planck's mandate correctly, then the experimental art of chemical thermodynamics with macromolecules is faced with a necessity for time consuming efforts. Only the first of the two integrals

$$\int_0^T \frac{\Delta C_p}{T} dT = \Delta S_T^0 \text{ and } \int_0^T \Delta C_p dT = \Delta \Gamma_T^0$$

is easily obtained from ΔH_T^0 and K or even from two measurements of heat at room temperature³. The second integral looks less complex than the first, but cannot be determined by any shortcut procedure. It is only possible to obtain it by measurements of ΔC_p at all temperatures between 0 K and T .

The treatment of $\int_0^T \Delta C_p dT$ as a negligible quantity is not a serious omission in ideal gas reactions, electron transport or other interactions of the smallest chemical entities. The contribution which our concept can make to the thermodynamic understanding of various kinds of chemical change is measured in differences between ΔH_T^0 and ΔH_0^0 and between $T\Delta S_T^0$ and $T\Delta\Phi_T^0$.

Numerical Differences

In the formation of water vapour from the elements in the gas state, for example, this difference is about 1%. The difference is, however, of order 10% for isomerization of an organic molecule of only five carbon chain length shown in Fig. 1, and for the formation of the double helix from single stranded polynucleotides shown in Fig. 2 the preliminary estimate of the difference is 100% or more. An even higher difference can be predicted from available data for the unfolding

of a protein after breakage of only a few bonds that hold the chain in its peculiar conformation (Fig. 3).

Our thermodynamic concept thus offers an explanation for heats of reaction of more than 8,000 calorie mol⁻¹ per base pair in Fig. 2; estimates for two hydrogen bonds per base pair would be much lower. The concept offers an explanation for the dramatic dependence of ΔH_T^0 on temperature observed in recent years in molecular biology. It is our conclusion that determinations of heat capacities ΔC_p down to the lowest attainable temperatures are indispensable for a future understanding of the thermodynamics of macromolecular change.

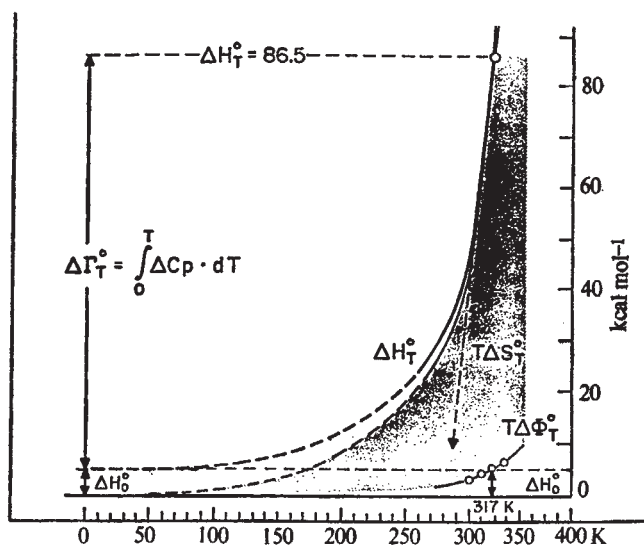


Fig. 3 Thermodynamics of protein unfolding (ribonuclease) using data measured by Danforth *et al.*⁶: midpoint of unfolding, 317 K; heat of unfolding, 86,500 calorie mol⁻¹ and "slope" of ΔH_T^0 against temperature $\Delta C_{p,317} = 2,300$ calorie mol⁻¹ K⁻¹.

Tentative plots of ΔH_T^0 or $\Delta \Gamma_T^0 = \int_0^T \Delta C_p dT$, $T\Delta S_T^0$ and $T\Delta\Phi_T^0 =$

$[T \int_0^T \frac{\Delta C_p}{T} dT - \int_0^T \Delta C_p dT]$ were obtained by extrapolation to zero slopes at 0 K as required by the third law. A tentative value of ~5,000 calorie mol⁻¹ is found for ΔH_0^0 , the energy of those few bonds that hold the chain of amino-acids in its peculiar, biologically active, conformation. (The experimental plot of ΔH_T^0 with the given slope at 317 K cannot be sensibly extrapolated to zero slope at 0 K with 86,500 calorie mol⁻¹ (broken straight line) as would be required if heat of reaction were taken for bond energy in classical fashion (see Pauling⁷). The graph of $T\Delta\Phi_T^0$ (circles) is based on $\Delta \Gamma_T^0$ values from optically determined, reactant and product concentrations (Danforth *et al.*). The slopes are experimental. The magnitude of ΔH_0^0 is tentative and subject to revision in the light of low temperature measurements of heat capacity differences.

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Mathematical Approach to the Prediction of Scientific Discovery

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In the field of symbolic logic at least, fundamental discoveries seem to follow patterns, suggesting that future discoveries may in some sense be predictable.

A SCIENTIFIC discovery $D = \{a, b, \dots, n\}$ may be modelled as a complete, ordered and finite set of permutable elements of information formed within the universe of scientific discourse. The elements of the set D may themselves be ordered sets of earlier scientific contributions. The act of discovery, then, might be regarded as a successful culmination of a series of efforts to acquire the necessary information elements and to find an appropriate set-defining and set-ordering criterion. The properties of the discovery set of completeness and order are apparent. The property of finiteness follows from the fact that the elements must be restricted to a manageable number. In other words, given that a discovery must be a product of human cognition which can be communicated and understood by other humans, it could not have been conceived and comprehended in the first place, nor could it have been communicated and categorized as a discovery if it were not reduced or abstracted to cognitively manageable dimensions, so that the set must be finite¹. The discovery process can thus be thought of as a process of set formation and transformation during inquiry and can be depicted as passing through four stages or states, which represent discrete points on a time continuum and thus do not describe the entire process of discovery.

Stage I. Insufficient and Unordered Information. At the outset of inquiry, a null set might exist. The domain of inquiry and the problem may be undefined or vaguely defined. Few, if any, elements of information will be available or, if available, have not been specifically designated as relevant to the inquiry. The problem is therefore to acquire information, not to order it. Once two or more information elements have been acquired, however, ordering problems appear. Although these elements may be arranged in different ways, their number may be insufficient to suggest an appropriate ordering.

Stage II. Insufficient but Ordered Information. A number of information elements have been designated tentatively as relevant to the inquiry. This number is sufficient to establish ordering relations and to imply bounds to the discovery set. The task thus becomes primarily one of ordering the information elements and increases in magnitude with the number of elements available.

Stage III. Sufficient but Unordered Information. As the acquisition of information continues, a sufficient number or even a surplus of information elements becomes available. At this point the bounds of the set are more apparent and may

be delimited as the elements are permuted. Nevertheless, a state of disarray still exists.

Stage IV. Sufficient and Ordered Information. The elements are reconstellated until a satisfactory discovery set D is obtained. The bounds of the set have been delimited so that the redundant or nonrelevant information is now excluded. Once the discovery set D is established, it may be elaborated, refined, or challenged by scientists who either support or oppose it. With the acquisition of new information or the revival of previously excluded elements the discovery set D may be partially or completely decomposed. Inquiry might then revert to states II or III or, in some cases, to state I. The cycle of acquiring and ordering information is then wholly or partially repeated in order to make a new discovery. A sequence of related discoveries culminates in the formation of a disciplinary system¹.

Such a process can be represented mathematically, as a four state Markov chain the state transition probabilities of which represent the probabilities of movement of a disciplinary system among the four states. If the Markov chain describing the development of a given discipline turns out to be ergodic, then by a well-known theorem on Markov chains², the reciprocals of the stationary probabilities are equal to the mean recurring times of the respective states. We may thus be in a position to predict the expected occurrence of each state, particularly state IV, the discovery state for the given discipline.

As an illustration, let us consider the development of the field of symbolic logic from 1847 to 1932, from the work of Boole and De Morgan to that of Gödel. Church in his definitive bibliography has provided a complete list of publications in this field during this period of time. Church has, moreover, marked with an asterisk³ "publications which are thought to be of special interest or importance from the point of view of symbolic logic", and with a double asterisk publications "which mark the first appearance of a new idea of fundamental importance"³. On the basis of Church's evaluation of these important publications, the four basic states in the discovery process for the field of symbolic logic during the period 1847–1932 can be operationally defined as follows (i ranging from 1847 to 1932):

(I) The system (symbolic logic) is said to be in state E_1 (insufficient and unordered information) in the year t_1 if no single or double asterisk publication appeared in that year, as documented by the Church bibliography.

(II) The system is said to be in the state E_2 (insufficient but ordered information) in the year t_1 if only one single asterisk and no double asterisk publication appeared in that year.

(III) The system is said to be in state E_3 (sufficient but unordered information) in the year t_1 if more than one single asterisk but no double asterisk publications appeared in that year.

(IV) The system is said to be in state E_4 (sufficient and ordered information) in the year t_1 if at least one double asterisk publication appeared in that year.

Estimates of the one step transition probabilities for these four states were obtained in the following manner. Let N_i be the total number of years that the system was in state E_i , $i = 1, 2, 3, 4$, and let N_{ij} be the number of times the system moved from state E_i to state E_j in the following year, $i, j = 1, 2, 3, 4$. Then N_{ij}/N_i was taken as an estimate of the probability p_{ij} of the system's transition from state E_i to state E_j . By carrying out these computations for all possible pairs of states, the following matrix of transition probabilities was obtained:

	E_1	E_2	E_3	E_4
E_1	0.53	0.21	0.21	0.05
E_2	0.50	0.18	0.23	0.09
E_3	0.21	0.35	0.26	0.18
E_4	0.37	0.37	0.26	0.00

Clearly, this Markov chain is irreducible as every state can be reached from every other state. Moreover, all states are ergodic, that is

$$\lim_{n \rightarrow \infty} p_{ij}^{(n)} = u_j > 0$$

with the following values:

μ_1	μ_2	μ_3	μ_4
0.44	0.25	0.23	0.08

Hence the mean recurring times for the four states were approximately 2.2, 4.0, 4.4 and 12.5 years for E_1 , E_2 , E_3 and E_4 respectively. Consequently, the system would be expected to pass through state E_4 , that is a new idea of fundamental importance would be expected to occur, about every 12.5 years. On the other hand, a multiplicity of important contributions would occur, on the average, every 4.4 years, a single important contribution every 4 years and nothing of importance every 2.2 years. It would appear, therefore, that the pathway between fundamental discoveries in symbolic logic did not follow an orderly pattern but passed through a sequence of cycles oscillating among states E_1 , E_2 , and E_3 until a discovery of fundamental importance eventually emerged. It is interesting to note, from the matrix of transition probabilities, that once the system entered state E_4 its probability of remaining there was zero. Hence fundamental discoveries had the property of immediately moving the system into a state of greater disorder. In other words, important new ideas seemed to pose more questions than they answered. On the other hand, the greatest uncertainty of movement occurred when the system was in state E_3 indicating that the final step of ordering a sufficient body of information into a discovery set was not straightforward but passed through a number of backward steps before reaching a successful culmination.

It has been shown previously that the development of a disciplinary system has common characteristics with the spread of infectious disease and can therefore be studied as an epidemic process⁴. Such analyses reveal that disciplines develop in a pattern resembling a sequence of overlapping epidemics, each one of which represents the rise and fall of particular areas of research activity. In treating a discipline as an epidemic process three classes of individuals are considered at any point in time. These are (a) those individuals who are actively contributing to the subject, (b) those who have contributed in the past and are no longer active and (c) those who may contribute to the subject in the future. In epidemiological terms these classes of individuals represent the infectives, removals, and susceptibles, respectively, of the epidemic process. We adopt the following general definitions:

(1) An individual is said to have become an active contributor (infective) to the field of symbolic logic in the year of publication of his first citation appearing in the Church bibliography.

(2) An individual is said to have been removed as an active contributor (removal) to the field of symbolic logic one year after the appearance of his last citation in the Church bibliography. On the basis of definitions (1) and (2), the epidemic

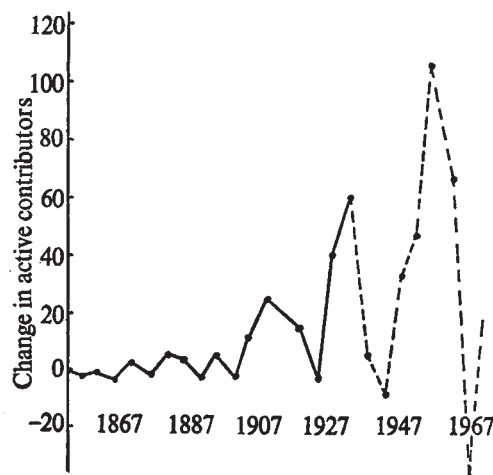


Fig. 1 Epidemic curve for symbolic logic.

curve for symbolic logic, that is the change in the number of active contributors to the field, in five year intervals for the period 1847–1932, was established as is shown in Fig. 1. We note that the field developed in a pattern resembling a recurring epidemic with peak points and initial points occurring at intervals of approximately twenty-five years. This would suggest that the disciplinary system passed through state E_4 at both the initial and peak points of the epidemic process; in other words, that fundamental contributions to the field both instigated and stabilized each epidemic outbreak. Inspection of the Church bibliography indicates that this was the case. For example, the work of Frege, Russell and others on the foundations of arithmetic and the relationship between logic and mathematics which led to the discovery of the paradoxes of set theory launched an epidemic of activity at the end of the nineteenth century which stabilized with the work of Zermelo about 12.5 years later. Approximately 12.5 years subsequent to Zermelo's fundamental work, Hilbert's programme for demonstrating the consistency of arithmetic by metamathematical methods resulted in a new outburst of activity which culminated in about 12.5 years with Gödel's incompleteness theorem again stabilizing the field.

By listing the material in the *Journal of Symbolic Logic Reviews* supplemented by the relevant items from *Mathematical Reviews* and *Zentralblatt für Mathematik* and by applying definitions (1) and (2), we can extend the epidemic curve for symbolic logic from 1932 to the present time. This extension is shown by the broken line in Fig. 1. We observe that the twenty-five year cycle was maintained for this discipline up to the present time. An epidemic outbreak occurred around 1942, peaked around 1957 and reached a low point around 1967. Hence the field should now be entering the initial stages of a new outburst of activity.

In conclusion, it would appear that, for the field of symbolic logic, fundamental discoveries followed predictable patterns. Events leading to the formation of a discovery set D took on the form of a sequence of oscillations among various states, each predictable in time, in an effort to acquire the necessary elements of information and appropriate ordering criteria which culminate in the act of discovery. The discipline was then built on a predictable sequence of discoveries. It is tempting to speculate as to whether similar patterns exist for every scientific discipline. This topic seems worth further investigation.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Are Protars Spinars?

MORRISON¹ has suggested that quasi-stellar radio sources and pulsars are basically similar phenomena, being analogues in every respect except scale. He has characterized both types of objects as centrally condensed magnetized spinning masses with a luminous lifetime which is governed by the rotational work done on charged particles by their moving magnetic fields. In the spirit of this hypothesis, Morrison has also proposed (private communication) that the name "spinar" be applied to objects such as quasi-stellar objects (QSOs), pulsars, and other highly condensed core objects which may exist in the nuclei of Seyfert galaxies and extragalactic radio sources.

I wish to point out a possible connexion between the hypothesis of Morrison and those of Harrison², Gunn and Ostriker³, and myself⁴, which may be of significance in the future.

Harrison⁵ has argued that galaxies cannot condense out of an initially homogeneous big bang universe. The existence of galaxies requires the existence of inhomogeneities imprinted on the metric from a time⁶

$$t^* = (Gh/2c^5)^{1/2} \simeq 4 \times 10^{-44} \text{ s} \quad (1)$$

Harrison therefore suggests² that, even during its earliest stages, the universe was structured with protogalactic configurations which were relatively dense and possessed spins. He argues that these "spinning cores" may have accounted for the origin of present galactic magnetic fields. They would thus fit Morrison's definition of spinars.

Gunn and Ostriker³ have shown that such "spinars" may be capable of accelerating cosmic ray protons to energies of the order of

$$E_{\text{max}} \sim \left[\frac{e^2}{Gm_p^2} \right]^{1/2} m_p \quad (2)$$

or $\sim 10^{21}$ eV. The cosmic rays themselves would be unobservable if produced at high redshifts, but secondary γ -rays produced by interactions of these cosmic rays would be observable out to redshifts of ~ 100 .

Indeed, such γ -rays, originating at a redshift ~ 70 – 100 , may have already been observed by Vette *et al.*⁷. I have suggested that the γ -ray evidence suggests such primordial cosmic ray sources⁴.

If we tentatively identify protars to be the spinars of an early epoch in the history of the universe, we arrive at a qualitative outline of a cosmology consistent with and suggestive of primordial inhomogeneities. Such a picture deserves further study.

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Atmospheric Dusts collected off the West African Coast

IN recent years several studies^{1–4} have revealed that wind-transported (eolian) dusts make a significant contribution to the land-derived material in some deep-sea sediments. This contribution depends, among other factors, on the amount of dust in the marine atmospheres, which can vary considerably from one area to another (Table 1). The greatest concentrations of dust have been found in the north-east trade winds over the North Atlantic Ocean. These winds receive a readily available supply of dust from the Sahara Desert, and have been sampled at Barbados¹ and Bermuda⁵. Few collections have been made in oceanic areas adjacent to the Sahara coast, however. We

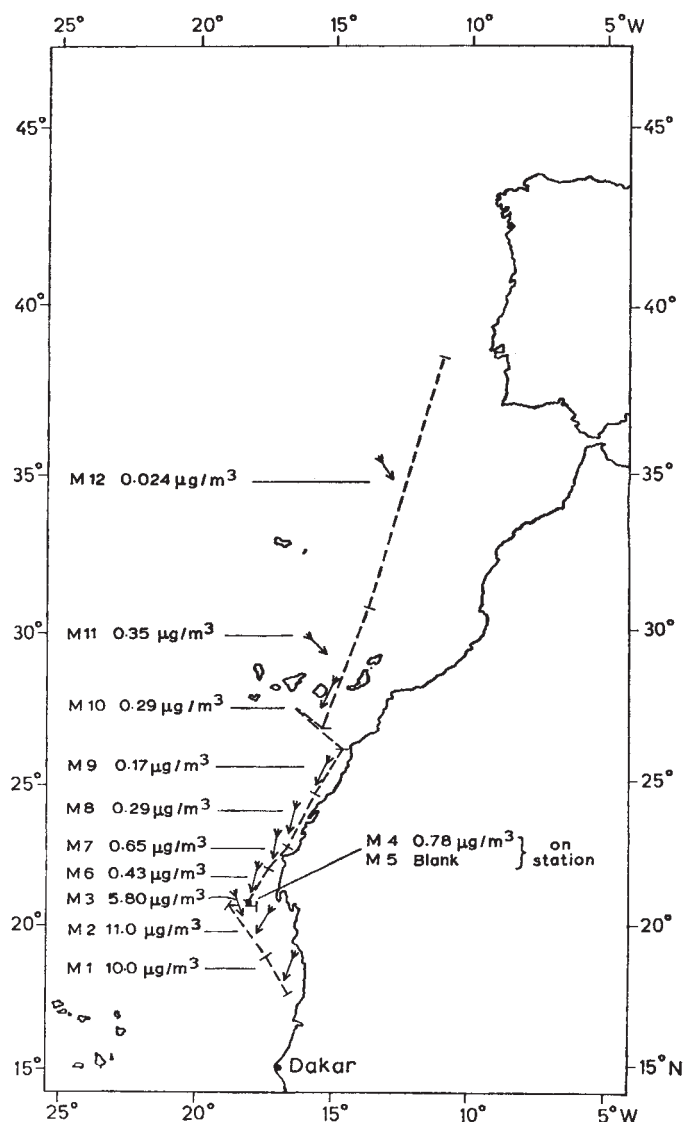


Fig. 1 Collections of atmospheric dust made on cruise 26 of RRS Discovery. The dashed line indicates the ship's track, and the arrows the relevant average wind direction. The sample reference numbers are given and the atmospheric dust load (calculated assuming a 50% mass collection efficiency).

Table 1 Eolian Dusts collected in Oceanic Areas

Ocean	Station	Time of year	Wind system	Amount of dust ($\mu\text{g}/\text{m}^3$ air)	Reference
North Atlantic	Shipboard	Winter	Westerlies	0.003	2
	Shipboard	Summer	Westerlies	0.003–0.03 (rising up to $4 \mu\text{g}/\text{m}^3$ air off the US coast, due to pollution)	2
North Atlantic	Barbados	Summer	N.E. trades	4	1
	Barbados	Winter	N.E. trades	0.6	1
	Bermuda	Summer	N.E. trades	6.5	5
	Shipboard, off West African Coast (in off-shore winds)	Spring	N.E. trades	10.5	Present work
North Pacific	Shipboard	Spring	Westerlies	0.5–1	4
North Pacific	Shipboard	Spring	Inter-tropical convergence zone	0.68	3
South Pacific	Shipboard	Spring	S.E. trades	0.14	3

wish to present the preliminary results of several collections made off the West African coast on board RRS Discovery, on the LUDO 9 Expedition (Discovery Cruise 26) undertaken by Liverpool University, Department of Oceanography, from April 22 to May 5, 1969.

The dusts were collected on nylon meshes, and the volume of wind passing through the meshes was calculated using a calibrated anemometer. Four meshes, each 1 m^2 , were exposed for each collection, and the weights of dust collected were corrected for the collection efficiency of the meshes, which was assumed to be 50%. The ship's track, the station positions, the directions of the prevailing wind and the amount of dust collected during the various runs are shown in Fig. 1.

In the first two exposures the wind was blowing directly from the desert areas of the African mainland, and the dust collected averaged $10.5 \mu\text{g}/\text{m}^3$ of air, which is an order of magnitude higher than those collected at Barbados¹ in the spring of 1966 (about $1 \mu\text{g}/\text{m}^3$ of air). At the remaining stations off the West African coast, however, the prevailing winds were long-shore, and on average carried $< 1 \mu\text{g}/\text{m}^3$ of air. It is evident, therefore, that average dust content of the north-east trade winds travelling across the Atlantic must be considerably less than $10 \mu\text{g}/\text{m}^3$ of air, and might approach the figure of $1 \mu\text{g}/\text{m}^3$ of air collected at Barbados.

The particle size analyses of the dusts M1 to M3, M4 to M10 and M11 to M12 are given in Table 2, and are compared with those of the land-derived material in several deep sea sediments adjacent to the African coast. In each comparison the dusts

Table 2 Particle Size Analyses of the Dusts and some Deep Sea Sediments

	Average of dusts M1, 2, 3	Deep sea sediment C1; $16^\circ 01' \text{N}$, $19^\circ 16' \text{W}$
2 μm	62	82.2
2–4 μm	11	3.3
4–8 μm	17	8.5
8–16 μm	7	4.4
16–32 μm	2.5	1.3
32 μm	0.5	0.3
	Average of dusts M4–M10	Deep sea sediment F7; $25^\circ 08' \text{N}$, $19^\circ 49' \text{W}$
2 μm	66	64.0
2–4 μm	22	13.6
4–8 μm	9	10.0
8–16 μm	2.5	6.6
16–32 μm	0.5	3.1
32 μm	—	2.7
	Average of dusts M11 and M12	Deep sea sediment 12; $33^\circ 52' \text{N}$, $19^\circ 07' \text{W}$
2 μm	57.5	79.4
2–4 μm	26.5	6.5
4–8 μm	10	12.0
8–16 μm	4	3.1
16–32 μm	1.5	—
32 μm	0.5	—

Size analyses of the dusts were made by a column settling technique and by microscopic counting. Those of the deep sea sediments were carried out by A. I. Beltagy.

Table 3 Mineralogy of the Eolian Dusts

Dust	Clay mineralogy * ($< 2 \mu\text{m}$ fraction)									$< 2 \mu\text{m}$ fraction						
	Montmorillonite	Illite	Kaolinite	Chlorite	Mica	Amphiboles	Chlorite	Calcite	Dolomite	Clino-pyroxenes	Haematite	Anatase	Rutile	Quartz	Plagioclase	K-feldspar
M1	16	46	23	15	Muscovite	x x	x x	x x	x x	—	x	x	x	x x x	x x x	x x
M2	7	57	23	13	x x Muscovite	x x	x x	x x x	x x	—	x	x	x	x x x	x x x	x x
M3	4	58	19	19	x x Muscovite	x		x x x	x x	—	x	x x	x	x x x	x x x	x x
M11	2	60		38	x x x	x		—	—	x x	x	—	—	x x x	x x x	—

Analyses were carried out by J. J. Griffin.

* The analyses are in terms of a 100% clay sample.

x Present. x x Abundant. x x x Very abundant.

Table 4 Clay Mineral and Quartz Contents of the Eolian Dusts and some Deep Sea Sediments

	Dusts			Deep sea sediments	
	M1	M2	M3	Barbados ¹	C2
				(16°01'N; 19°16'W)	(16°02'N; 29°46'W)
Montmorillonite	16	7	4	16	24
Illite	46	57	58	41	18
Kaolinite	23	23	19	32	46
Chlorite	15	13	19	10	12
Quartz	20	20	ND	10	15.5

ND, Not determined

Clay mineral analyses are for the <2 μ m fractions of the dusts and sediments. They were carried out by J. J. Griffin, and are expressed in terms of a 100% clay sample. Quartz analyses are for the total sediment and dust samples. Those for the dusts were made by us, those for the sediments by A. I. Beltagy.

contain a greater percentage of material in the 2–8 μ m size class than the sediments, and a smaller percentage in the <2 μ m size class. This probably reflects the fact that the collection efficiency of the meshes decreases with decreasing particle size¹.

The mineralogical analyses of several of the dusts are given in Table 3. Quantitatively, the most important minerals in the dusts, and in the land-derived fractions of deep sea sediments, are the clay minerals and quartz. Table 4 shows that the West African dusts contain less kaolinite and more illite than both the deep sea sediments and the average Barbados dust, although the mineralogy of deep sea sediment C2 is very similar to that of the dust M1. The quartz contents of the dusts is greater than that of both the deep sea sediments and the Barbados dust. This is because quartz is present chiefly in the larger size fractions of the West African dust, and much of it will have fallen out by the time the wind mass reaches Barbados.

Although the exposures M1 to M10 were made in the general area of the north-east trade winds, meshes M11 and M12 were exposed in the boundary region between these winds and the westerly winds. Table 2 shows that the mineralogies of the north-east trade and the "boundary" dusts are significantly different, particularly in their content of minor minerals. For example, dolomite is a characteristic mineral in the dust of the north-east trades¹, and although it is present in samples M1 to M10 it is absent from M11 and M12.

We thank the master, officers and crew of RRS Discovery for their cooperation, Dr D. W. Parkin, of the University of Bath, for the meshes, and Dr J. J. Griffin, of Scripps Institution of Oceanography, for carrying out the mineralogical analyses.

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Stratospheric Properties and Bali Dust

NEWELL has drawn attention to an anomalous increase of about 5° C in the stratospheric temperatures in tropical and mid-latitudes in the Southern Hemisphere since 1963. He

suggested a causal relationship between this increase and the eruption of Mount Agung in March 1963, which injected large quantities of volcanic material into the stratosphere². I wish to draw attention to several publications which have shown that at the same time a breakdown occurred in the quasi-biennial oscillation. This should be considered before Newell's conclusion can be accepted.

I have proposed tentatively³ that the temperature anomaly was related to the effects of the Bali volcanic debris or to a change in the nature of the quasi-biennial oscillation. Evidence for the breakdown of the biennial oscillation in total ozone amount and lower stratospheric temperature during this period has been presented by Kulkarni⁴ and by Berson⁵. Berson and Kulkarni⁶, following Ramanathan⁷, have shown that previous changes in phase of the quasi-biennial oscillation have occurred during solar minima, suggesting the breakdown occurring in 1963 may similarly be related.

The question of solar control over the phase changes in the quasi-biennial oscillation is relevant to a discussion of the effects of the Bali injection into the stratosphere. Would an increase in temperature of 5° C have occurred and the temperatures remained above normal for several years if Bali had erupted, say, 5 yr earlier, or was the magnitude of the temperature change related to some combination of the effect of the Bali dust and the change taking place in the phase of the quasi-biennial oscillation? Alternatively, did the dust injected into the stratosphere trigger the changes in the oscillation? Until the interaction and magnitude of the two effects can be separated out, it seems somewhat doubtful to equate the 5° C temperature change entirely to the presence of the Bali dust as Newell has done.

It is assumed that the temperature observations reported by Newell are for 2300 h GMT for the Australian stations (approximately 10 a.m. local Australian EST), for night time observations have been taken at (some) Australian stations continuously only since late in 1962. This is unfortunate because an increase in stratospheric temperature due to particle absorption of sunlight might be expected to lead to an enhancement in the diurnal temperature changes at the same height. Diurnal temperature changes at 60 mb in the tropics are of the order of 1°–3° C.

However, examination of the records for US stations in tropical regions have previously failed to show any evidence of a change in the twelve hour temperature differences occurring in 1963 and 1964 (ref. 8). The stations studied included Ascension Island (8° S, 15° W) at the same latitude as Mount Agung. On the other hand, the quasi-biennial oscillation has not been seen in the diurnal temperature differences prior to 1963, nor would it be anticipated that it should occur after this time.

As Newell pointed out, the study of any modification in stratospheric properties due to the presence of volcanic material has important practical applications to the future use of the supersonic transports. The Bali eruption is perhaps the only large eruption for which a reasonable amount of meteorological data is available⁹. It is unfortunate therefore that so little use has been made of such a potentially powerful means of studying stratospheric properties.

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Rainfall at Sea

DURING the winter 1969–1970 we installed an 8 inch tipping-bucket recording rain gauge on a large spar-buoy, Totem, located at 45° 04' N latitude 124° 44' W longitude. This is about 56 km west of Cascade Head, Oregon. The water caught in the gauge was retained on the buoy and measured at intervals of approximately 1 month. Four such measurements of total rain were collected between November 22, 1969, and April 6, 1970. Table 1 gives the measured rainfall at the buoy for these four periods, as well as measured rainfall at selected sites on the Oregon coast. During two of the periods the rain gauge recording functioned properly and we were thus able to obtain a chronology of the rainfall.

Table 1 Rainfall (mm) at Selected Stations, Winter 1969–70

Location	Nov 22– Jan 10	Jan 10– Feb 4	Feb 4– Mar 8	Mar 1– Apr 4
Totem	107	111	65	64
Newport	459	433	200	122
Otis	455	568	201	192
Nehalem	466	713	192	255
Astoria	324	360	125	217
Wecoma Beach	—	—	179	139
Corvallis (Island)	307	376	143	58

The differences between the rainfall measured at Totem and at the coast have many implications for oceanography and the atmospheric sciences. In some estimates of rainfall over the ocean a coastal effect has been suggested. Wüst² feels that an overall 20% reduction in coastal values is necessary, and Jacobs³ reduced estimates for the Pacific based on extrapolated coastal values by 45%. The average reduction in Table 1 is about 71%, that is, the presence of the coast increased the rainfall by a factor of 3.5. This figure is only valid for coastal Oregon and the enhancement here may be much greater than at some other location around the Pacific. Clearly these data contradict the conclusion of Malkus⁴ who felt that little or no coastal enhancement would be found, particularly in areas where rainfall comes largely in cyclonic storms as it does in Oregon.

The types of storms affecting the Oregon coast are not radically different from those affecting the north-west coast of North America from California to Alaska. Indeed, Southern Chile and the coast of Norway are similar in climate and topography to coastal Oregon. Thus the effects noted off Oregon may well be found off several coasts. If these results hold true for areas of similar climate and conceivably for all the shores, then world-wide estimates of rainfall over the sea will have to be revised with consequences for studies of oceanic water budgets as well as the general circulation of the atmosphere. The most likely cause for this coastal increase seems to us to be found in the convergence accompanying the increased friction as the storms move inland. The resulting upward air motion may influence the storm cloud system or may create a new low cloud through which rain drops from the upper cloud pass and collect more water by coalescence. Clearly this effect should be studied in greater detail.

Anyone familiar with the difficulties of obtaining accurate measurements of rainfall on land, let alone at sea, will wonder whether Table 1 shows results of errors of measurement and exposure of the gauges. (Many problems are discussed in ref. 5.) We shall therefore discuss the possibilities for errors in measurements.

The rainfall measurements made on shore were all taken from US Weather Bureau stations, either first-order or co-operative, with the exception of Wecoma Beach. On Totem, the 8 inch tipping-bucket gauge was suspended inside a 50 gallon barrel which was mounted on the west side of the buoy about 11 m above the water line. The mouth of the gauge was essentially level with the mouth of the barrel and the gauge was suspended by springs with a weight added at the bottom.

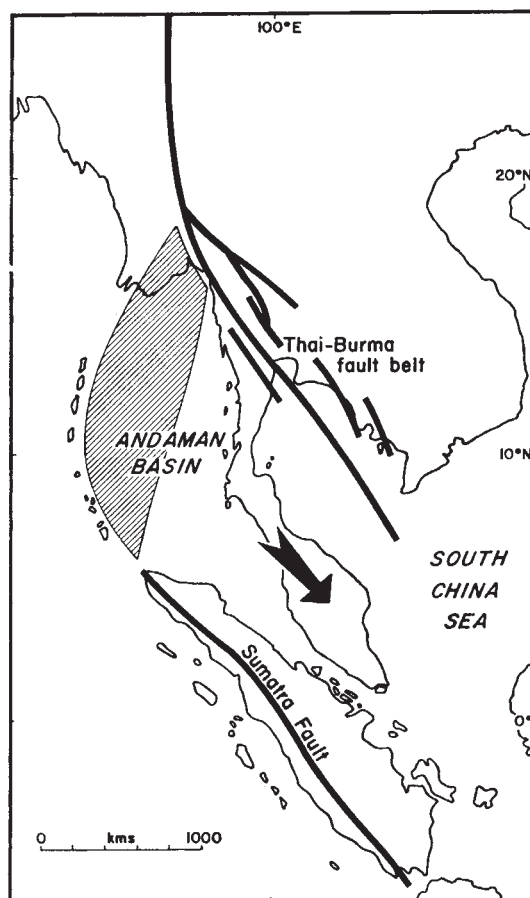


Fig. 1 Location of observing stations given in Table 1.

These steps were taken to minimize vibrations of the gauge to lessen the chance of early tipping of the buckets. In addition, during the last two periods, a 10 inch non-recording gauge was mounted on a pole suspended from the buoy at about the same height as the other gauge. No special precautions were taken with this instrument. Both gauges were modified to permit their catches to drain into containers which could be returned to shore for analysis.

The data reported for Wecoma Beach in Table 1 came from an identical tipping-bucket gauge mounted inside a similar barrel which was installed in early February. Also at this location a standard 8 inch gauge was installed and read daily. No differences of more than 5% between these two gauges were found for any given day. Thus we conclude that the configuration of the gauge in the barrel has negligible effect on the differences noted in Table 1.

When the water was returned to the laboratory its salinity was measured to determine whether it contained significant quantities of spray. No salinity greater than 1 p.p.m. was measured, and so we feel safe in neglecting this factor. We also checked whether evaporation could be reducing our apparent catch. We left on the beach a measured quantity of water in a container similar to ones used to retain the catches at sea. No change in quantity was detectable after a month of exposure so we feel safe in ignoring evaporation as a cause of the low catches at sea.

Catches made in rain gauges are notoriously sensitive to wind speed, and high wind can reduce the catches significantly. It is possible that the gauges 11 m above the sea were subjected to much higher winds than the gauges on shore. A check of the few wind speeds reported from the oceanographic research vessels which were operating in the vicinity reveals no systematic variation during the period of observation. On some days winds were much higher at sea than on the coast, but on others the reverse was true, and on some days winds seemed to be about the same in both cases.

Another possible source of error is the buoy itself. The motions of the buoy could affect the catch and the buoy itself could distort the wind field and so reduce the catch. The buoy is designed to move very little; it does not tilt more than 10° even in heavy seas. Nor does it rotate very rapidly at all. It seems to be a stable instrument platform and much better than a ship.

One further set of observations supports our contention that there is less rainfall at sea. During January 16 to 21, 1970, Oregon State University's RV Yaquina was cruising between 44.5° and 46.0° N latitude at about 126.5° W. This line extends from about the latitude of Newport to a point 100 km north of the Totem position and is about 160 km west of the Totem position. During this cruise the ship took the standard ship's weather observation which includes an assessment of the present weather (ww code) and the weather in the past 6 h (W code) (no quantitative measurements of precipitation are made from ships). For this period we also have a time record of precipitation from the Totem, so an assessment of the daily rainfall there is possible.

Sawyer⁶ has presented a scheme whereby the reported "present weather" can be converted to precipitation amounts. Applying his conversions of reported weather to obtain hourly precipitation rates and assuming they were valid estimates for the 6 h period between observations (this is apt to be an overestimate of the duration), we obtain an estimated total of 27 mm for the rainfall recorded aboard Yaquina. An amount of 20 mm was recorded at Totem but 160 mm was recorded at Newport. Thus during this particular week much more rain fell on the coastal land area than over the adjacent sea. This lends weight to the contention that these observations strongly support the thesis that coastal rainfall is much greater than rainfall over the open ocean; perhaps by a factor of two to four.

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New Method for measuring Density of Seawater

SEAWATER density, a property of fundamental importance for oceanographers, is usually calculated from salinity (determined by chlorinity titration or measurement of electrical conductivity) using Knudsen's hydrographical tables¹. These tables of relationships between salinity, temperature and density are based on the results of only twenty-four seawater analyses². Recent investigations, especially by Cox, MacCartney and Culkin³, have shown good agreement with Knudsen's tables in the salinity range $S^\circ_{00}=15-40$. For water of low salinity such as the Baltic Sea, however, there are greater discrepancies

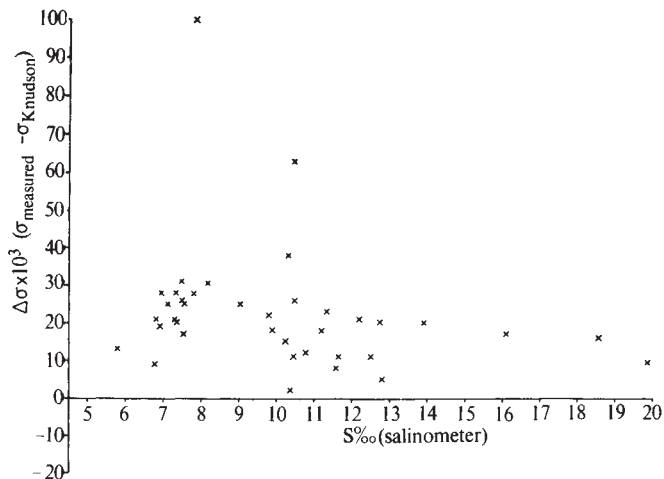


Fig. 1 Baltic Sea, spring 1966. Temperature, 20° C.

caused chiefly by variation of ionic relationships. No detailed investigations have been made so far, because of the difficulty of making very accurate density measurements.

A new apparatus, constructed by Kratky, Leopold and Stabinger⁴ (A. Paar KG Company, Graz-Strassgang, Austria), determines density electronically, making density determination both accurate and rapid. A hollow, glass, bending oscillator (2 mm in diameter) is excited into undamped oscillation. When the system is filled with the sample, the resonant frequency of the oscillator is influenced by the mass, and therefore by the density of the sample.

The volume, V , taking part in the oscillation is defined by two fixed oscillation points. The period of the system with mass M and the spring constant, C , of the hollow body and the density d of the sample inserted into the system is thus

$$T = 2\pi \sqrt{\frac{dV + M}{c}} \quad (1)$$

We take the square and insert

$$A = \frac{4\pi^2 V}{c}; \quad B = \frac{4\pi^2 M}{c}$$

to give

$$T^2 = Ad + B \quad (2)$$

For the difference of the densities of two samples

$$d_1 - d_2 = \frac{1}{A}(T_1^2 - T_2^2) \quad (3)$$

The apparatus constant, A , which is dependent on temperature can be determined by two calibration measurements with samples of known density.

For standard 1 we take air of which the density can be calculated to about $\pm 0.6 \times 10^{-6} \text{ g cm}^{-3}$; for standard 2 we use distilled Mediterranean seawater from a depth of 2,200 m, of which the constant isotopic composition is well known and is scarcely influenced by distillation⁵ (density values are taken from Thiesen *et al.*⁶). The length of a preselected number of time periods is measured by a crystal-controlled timer in units of 10^{-5} s . The time needed for oscillation of seawater (35°_{00}) is about 46 s. The temperature equilibration of the sample is an important factor. When the measurement was made at a low temperature the insulation of the installed oscillatory system was inadequate, but when this had been improved it was possible to keep the temperature at $\pm 0.005^\circ \text{ C}$. The half-time of equilibrating is about 1 min, and the whole procedure can be completed in 15 min. The sample volume needed is only 0.6 cm^3 . The oscillatory system is filled by means of a plastic syringe which is inserted precisely into the

glass tube. The introduction of a larger volume than is needed for oscillation prevents evaporation during measurement and makes the operation very easy.

The standard deviation at 5° and 20° C—obtained by ten replicate measurements of Baltic seawater (including the whole procedure)—is $\pm 2.5 \times 10^{-6} \text{ g cm}^{-3}$. Deviations from this value can be caused by suspended particles and bubbling during measurement.

Preliminary density data obtained by this method are given in Fig. 1, where the differences between the measured and calculated densities at 20° C are plotted as a function of salinity. Calculated densities from Knudsen's tables are based on salinities determined by conductivity, which in the Baltic are in good agreement with actual salinity and Knudsen's equation $S_{\text{‰}} = 1.805 \text{ Cl}_{\text{‰}} + 0.03$ (ref. 7). The samples were taken in 1966 in the Baltic at seventeen different stations. The deviations are about $20\text{--}30 \times 10^{-6} \text{ g cm}^{-3}$ ($0.02\text{--}0.03 \sigma_t$) in lower salinity regions and decrease slightly in regions of high salinity. But in some samples considerable deviations are detected, with a maximum of $0.1 \sigma_t$ in the surface water of Arkona Basin. These anomalies, which cannot be recognized by indirect methods involving, for example, salinity, are probably caused by pollutants which, although they influence conductivity only slightly, could have a considerable effect on density.

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Frequency of the Hydrogen Maser

THE accuracy of the unperturbed frequency of the hydrogen maser is limited by the uncertainty of the wall shift caused by the storage bulb coating¹. Different samples of nominally the same material have been found to give different shifts² and so it seems that a frequency determination should include an independent measurement of wall shift. The results of such determinations^{3–7}, however, have a spread of 0.018 Hz which is large compared with the potential accuracy of the maser. The wall shift depends on the number of bounces of the atoms on the wall of the bulb and for a spherical bulb can be expressed as K/D where K is a constant for a particular coating material and D is the diameter of the bulb. If measurements are made with bulbs of different size and the frequency is plotted against $1/D$, the true frequency is that corresponding to infinite bulb size, that is $1/D=0$, and the slope of the line gives the constant K . The range of bulb sizes that can be used is limited by practical considerations and there is therefore an extrapolation error in addition to the error of measurement. This extrapolation error can be reduced by making measurements with two different coating materials and making the assumption that the values should coincide at $1/D=0$.

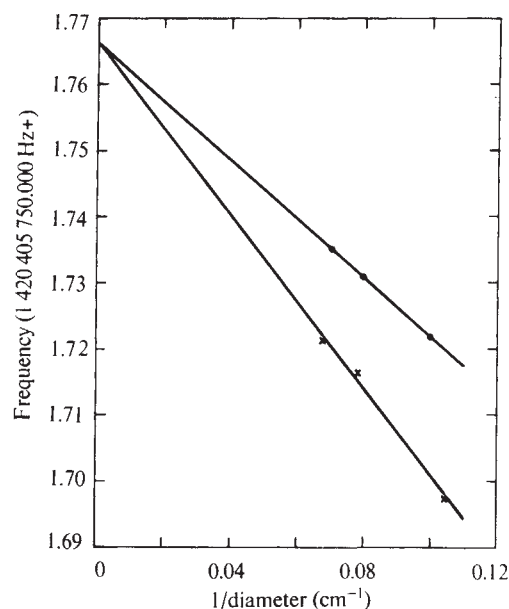


Fig. 1 Variation of frequency of hydrogen maser with size of bulb. ●, Coating material 'Teflon FEP 120'; ×, coating material 'Fluon GP1'.

Three bulbs were coated with 'Teflon FEP 120' and three with 'Fluon GP1'. The frequencies of the maser were measured in terms of the NPL unit of time which is based on several commercial caesium and rubidium clocks and the NPL (National Physical Laboratory) long caesium beam standard.

The results are shown graphically in Fig. 1, in which the lines are drawn to give the best visual fit between the observed points and the mean of the computed intercepts at $1/D=0$. These computed values were 1 420 405 751.766 3 Hz for 'Teflon FEP 120' and 1 420 405 751.767 1 Hz for 'Fluon GP1'. The frequency of the maser, unperturbed by wall collisions, is estimated to be

$$f_H = 1\,420\,405\,751.766\,7 \pm 0.001 \text{ Hz}$$

In accordance with current practice the observed values were corrected for the second order Doppler shift. It has been suggested that there is an additional frequency shift due to collisions between the hydrogen atoms^{8–11}, but that this shift is compensated by an offset in the cavity tuning, if this is set to make the frequency independent of the pressure of hydrogen in the bulb. In our experiment the cavity tuning was set to two values which gave equal amplitudes of oscillation slightly less than the maximum, and the mean frequency was taken as the maser frequency. This method was sensitive, quick and simple, but if it corresponds to setting the cavity frequency exactly to the maser frequency, then there might be a shift due to interatomic collisions. To check this, the hydrogen pressure was varied throughout the range for which stable operation was maintained and the frequency measured as described above. The maximum deviation was only 0.0007 Hz although the pressure change was at least ten times as great as would occur in normal operation. It was decided that the method of setting was quite satisfactory for defining the frequency, and as there was no evidence of a significant shift due to interatomic collisions no correction has been applied.

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Neutron Diffraction by a Piezoelectric Resonator

It has been reported in neutron diffraction measurements that the neutron detector signal is enhanced and can be modulated when the diffraction crystal is piezoelectrically vibrated at a resonance frequency¹⁻⁹. The time averaged enhancement is an increasing function of vibration amplitude and the modulation is at twice the resonator frequency.

Several qualitative explanations of these phenomena have been advanced, mostly based on previous treatments of a related effect found in the diffraction of X-rays^{10,11}. Recently, a detailed analytical study of neutron diffraction by piezoelectric resonators has been presented^{12,13}. In this study the general form of crystal strain during vibration is assumed uniform throughout the crystal. For the high-frequency (of the order of MHz) resonators used in many of the measurements, a more accepted representation of crystal strain is a standing wave¹⁴. For example, the crystal strain in a plate vibrating in the longitudinal mode at the fundamental resonance frequency is a standing wave with wavelength equal to twice the crystal thickness. If such location-dependent strains are used in the analysis of diffraction of neutrons by a piezoelectric resonator, the explanation of the enhancement and modulation of the neutron detector signal is quite different from that generated by the assumption of uniform strain.

We report here a theoretical and experimental treatment of neutron diffraction from a crystal plate vibrating in the funda-

mental longitudinal mode¹⁵. The particular case treated and crystal used in this work is an X-cut quartz crystal, $2 \times 2 \times 0.220$ inch, with longitudinal vibration in the thickness direction and diffraction from the vibrating planes.

The assumptions made for the purpose of the analysis are: (1) There is no variation in the amplitude of vibration over the crystal plate surface. (2) There is no vibration in other than the thickness direction of the crystal plate. (3) The detailed relative motion of the atoms of a unit cell of the crystal is negligible. (4) Within the limits of the incident collimator the incident neutrons are isotropic, and within the energy range of interest there is no variation of neutron intensity with energy. (5) The crystal plate is considered static with an arbitrary amplitude of the strain standing wave for calculating the general form of the intensity function.

Assumptions 1-4 are reasonable by effective design of the neutron collimators and the crystal plate holder. Assumption 5 represents a large departure from the previous theoretical considerations of these phenomena. The implied neglect of phonon-neutron energy exchange is appreciated by the authors and can be included with an attendant complication in the calculation. The purpose here is to demonstrate clearly the strictly geometric aspects of the enhanced crystal diffractivity.

An Ewald sphere construction illustrates the conditions for diffraction within the context of the reciprocal lattice¹⁶. An Ewald construction for the quiescent crystal is shown in Fig. 1a. The incident neutron wave vector, s_0/λ , and diffracted neutron wave vector, s/λ , are indicated. Diffraction is by the planes represented by the lattice point M.

Calculation of the intensity function of the vibrating crystal is accomplished with the assumed static crystal distortion. It can be shown that the reciprocal lattice points of the undistorted crystal case becomes lines perpendicular to the vibrating crystal planes in the distorted crystal case¹⁵. This is shown in Fig. 1b for the particular diffracting planes considered here. The line M'M'' grows symmetrically from the lattice point as the vibrating crystal passes through the quiescent configuration to a length proportional to the amplitude of the crystal distortion at a given time. The frequency of oscillation of this line is thus twice the drive frequency of the crystal.

The angle 2α of Fig. 1b represents the collimation of the incident beam. Thus, neutrons with incident wave vectors initiating within the cross-hatched area of the example shown satisfy the conditions for diffraction. The ratio of this area to the area corresponding to the case of the quiescent crystal, when corrections are made for the effect of the crystal surface mosaic structure, gives the amplification of crystal diffractivity at any time during the vibration.

Fig. 2 shows the amplification of diffraction as predicted by theory and as determined by the experiment with a $2 \times 2 \times 0.220$ inch X-cut quartz crystal vibrated at a longitudinal mode

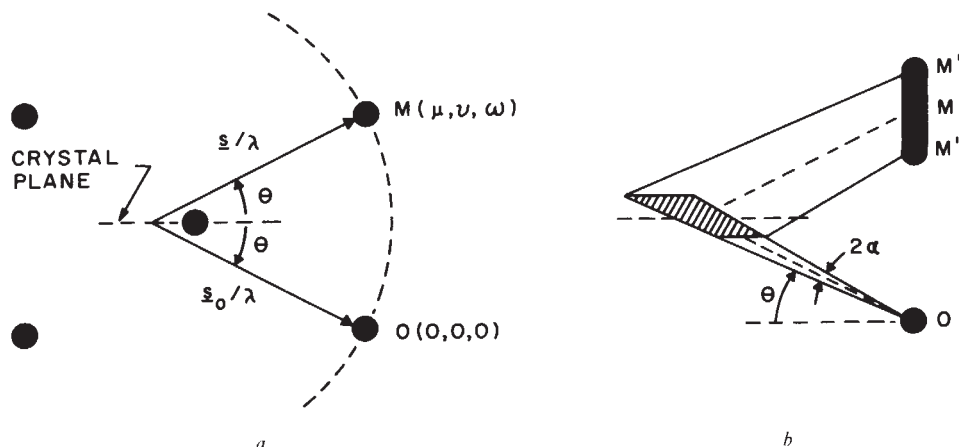


Fig. 1 Ewald sphere construction. a, Quiescent crystal; b, distorted crystal.

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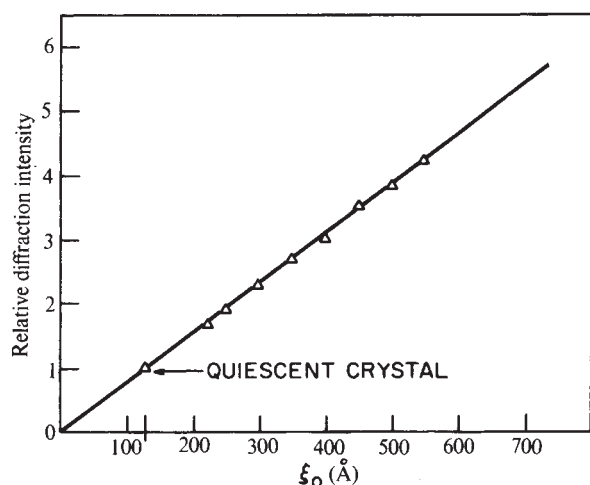


Fig. 2 Predicted (—) and experimental (Δ) amplitude of diffraction.

fundamental frequency of 500 kHz. The quiescent crystal case is assigned an equivalent vibration amplitude to account for the finite area of the quiescent reciprocal lattice point and its corresponding cross-hatch area of Fig. 1b.

It has been found that, for this case, the amplification results chiefly from a wider range of incident directions of neutrons which satisfy diffraction conditions when the crystal is vibrating. Less than 1% of the increase arises from a wider wavelength band¹⁵. This has been qualitatively confirmed by an experiment using a neutron chopper and time-of-flight techniques to analyse the energy dependence of the diffracted beam. Although the resolution of the experiment was insufficient to give quantitative results, it was clear that the intensity of the diffracted neutrons with wavelengths in the diffraction band was greatly enhanced by vibration, and that there was an insignificant increase of width of the diffracted wavelength band¹⁵.

The results of our measurements are in total agreement with the geometric interpretations just outlined. They are not consistent with the theoretical analysis based on the assumption of a uniform crystal strain in a piezoelectric resonator.

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Effect of Prostaglandin E₁ on Clot Retraction

ONE of the many properties of prostaglandin E₁ (PGE₁) is that it inhibits the aggregation of blood platelets in plasma at $\mu\text{g/ml}$. platelet-rich plasma¹⁻³, and of ADP-induced adhesiveness at the same low concentration^{1,2}. Emmons *et al.*¹ have also shown that platelet plug formation is prevented *in vivo* during infusion of PGE₁. Because of this we decided to investigate the effect of PGE₁ on clot retraction.

Three types of clot were studied. For type 1, 4 ml. platelet-rich plasma from citrated human blood was added to 1.5 ml. 0.1 M Tris-HCl buffer (pH 7.4) and 0.4 ml. of 0.31 M NaCl. Clot formation was started by the addition of 5 NIH units bovine thrombin ('Topostasin', Hoffmann-La Roche, Basle) and followed in a graduated glass tube incubated in water-bath at 37° C. For type 2, about 5 mg human platelets washed twice with saline containing ethylenediaminetetraacetate (pH 7.4) were suspended in 0.14 M NaCl—25 mM Tris-HCl (pH 7.4)—5 mM CaCl₂ in a total volume of 6 ml. Human fibrinogen (3 mg, fraction I-0⁴) was added and clotting was started with 5 NIH units thrombin as above. For type 3, a solution of fibrin monomers in 1 M KBr in 0.3 M acetate buffer (pH 5.3) was prepared according to the procedure described by Solum⁵. Fibrin monomers from fraction I-0 fibrinogen (0.8 g protein) were dissolved in a total of 2 ml. of the KBr solution. About 5 mg washed human platelets were suspended in 0.12 M NaCl—25 mM Tris-HCl (pH 7.4)—5 mM CaCl₂ and 5 antithrombin units (ATU) hirudin (VEB Arzneimittelwerke, Dresden). The fibrin monomer solution (0.2 ml.) was added to make a total volume of 6 ml., and a clot formed within seconds when incubated at 37° C. PGE₁ was applied as a 0.2 mg/ml. ethanol solution immediately before addition of thrombin. The high concentration of PGE₁ was necessary to ensure maximal effect, although in some cases this was achieved with a concentration of 70 ng/ml. incubation medium.

The retraction of the clot was followed for 50 min with type 1 and 20 min with types 2 and 3 in the experiments reported in Table 1. The clot was then removed and the change in volume was taken as the volume of the retracted clot.

Table 1 Effect of PGE₁ on the Retraction of Different Types of Clot

Expt.	Volume of retracted clot (ml.)								
	Type 1			Type 2			Type 3		
PGE ₁ (μg):	0	1	4	0	1	4	0	1	4
1	0.4	2.8	5.3	0.2	0.3	0.3	0.3	0.2	3.2
2				0.3	0.3	0.2	0.6	1.0	2.9
3	0.3	1.3	3.2	0.2	0.2	0.2	0.7	2.4	4.9
4	0.3	4.3	5.2				0.3		4.3

Table 2 Reversal by CaCl₂ of the PGE₁-induced Inhibition of Retraction of Type 1 Clots

Expt.	Volume of retracted clot (ml.)						
	PGE ₁ (μg):	0	4	4	4	4	4
CaCl ₂ added (μmol):	0	0	10	15	20	30	40
1 (63 min)	0.4	5.0	5.1		1.7	1.5	1.6
2 (50 min)	0.3	4.9	4.6		3.7	1.6	
3 (63 min)	0.3	4.7	4.6		4.8	2.0	2.0
4 (33 min)	0.2	2.8		3.5		0.3	
5 (33 min)	0.4	5.0		4.5		0.5	

The experiments were performed in the same manner with different preparations. The difference in degree of reversal of inhibition may indicate an effect of PGE₁ on platelet metabolism in addition to the direct effect on clot retraction. Numbers in parentheses give incubation time.

The results show that clot retraction is inhibited by PGE₁ in citrated platelet-rich plasma (type 1), and also in a suspension of washed platelets in buffered saline where the clot is formed by dilution of fibrin monomers in the presence of calcium (type 3). PGE₁ did not inhibit retraction of type 2 clots (Table 1). Addition of calcium to a total level of approximately 1 mol/mol anticoagulant reverses the inhibition of PGE₁ on retraction of clots prepared from citrated platelet-rich plasma (Table 2), but not of those prepared from fibrin monomers (Table 1).

Two apparent different types of inhibition are therefore exerted by prostaglandin E₁, one of which could be counteracted by calcium ions, and one which seemed to depend on the conditions for formation of the fibrin clot.

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Decreased Proliferative Activity of Erythroblasts in Granulocytic Stem Cell Leukaemia

PROOF of reduced reproductive activity of both leukaemic blastocytes in granulocytic stem cell leukaemia and of erythroblasts in Morbus Di Guglielmo² has previously been obtained using ³H-thymidine (³H-dThd) incorporation, microspectrophotometric measurements of DNA content and evaluations of mitotic indices. But no data have been published concerning ³H-dThd incorporation and mitotic activity of erythroblasts in patients suffering from granulocytic stem cell leukaemia. Such data are presented here.

Nine patients with granulocytic stem cell leukaemia (one erythroleukaemia, four myeloblastic and four promyelocytic leukaemias) and six healthy controls were studied. Cytochemical staining techniques confirmed the diagnoses (for method see ref. 3).

Heparinized blood of the bone marrow was diluted in a one to one ratio with tissue culture medium TC 199 and incubated at 37° C with ³H-dThd (s.a. 5,000 mCi/mmol) 1 µCi/ml. for 1 h. Autoradiograms were prepared from smears of bone marrow particles with Ilford G5 emulsion using the dipping technique. After 7 days of exposure at 4° C the autoradiograms were developed, fixed and stained with Giemsa at pH 5.75. From each of the leukaemia patients and the controls the following values were counted: ³H-dThd labelling index of 500 red cell precursors (from proerythroblasts to orthochromatic normoblasts); ³H-dThd labelling index of 500 white cell precursors (from myeloblasts to metamyelocytes); and the mean grain counts of the polychromatic normoblasts. The duration of DNA synthesis is assumed to be the same for normal and leukaemic subjects. The radioactivity counts of both were found to be similar. Further, in bone marrow preparations smeared immediately after biopsy, mitotic indices of 3,000 to 5,000 erythroblasts capable of division were counted. In order to avoid uncertainties in

identifying prophases, only meta-, ana- and telophases were evaluated.

The ³H-dThd labelling index of erythroblasts in cases of untreated granulocytic stem cell leukaemia was approximately only one third of that of the healthy controls ($P < 0.001$); whereas the two leukaemia patients in remission did not differ from the normals (Table 1). This result was in agreement with microspectrophotometric measurements of the DNA content of erythroblasts in stem cell leukaemia previously reported⁴. A significant reduction in the number of cells undergoing DNA synthesis was found only in the intermediate stages of maturation (Table 2). It is perhaps significant that the ³H-dThd labelling index of the erythroblasts in our patient suffering from erythroleukaemia was not less than that of the other leukaemia patients as would be expected. The mitotic index of erythroblasts in untreated stem cell leukaemia patients was approximately one half that of the controls ($P < 0.01$); in contrast the two leukaemia patients in remission did not respond differently from the normals (Table 1).

Table 1 ³H-Thymidine and Mitotic Indices, Mean and Standard Error

	³ H-Thymidine labelling indices (%)		Mitotic indices (%) Red cell precursors capable of division†
	White cell precursors *	Red cell precursors †	
Normal persons <i>n</i> = 6	19.6 ± 1.2	31.1 ± 0.74	32.0 ± 0.58
Leukaemics in remission <i>n</i> = 2	20.5	34.0	33.0
Untreated leukaemics <i>n</i> = 7	6.1 ± 2.0	11.3 ± 2.17	17.2 ± 2.63

* From myeloblasts to metamyelocytes.

† From proerythroblasts to orthochromatic normoblasts.

‡ From proerythroblasts to polychromatic normoblasts.

Table 2 ³H-Thymidine Labelling Indices of Erythroblasts in Different Stages of Maturation, Mean and Standard Error (%)

Stages of maturation	Normal persons <i>n</i> = 5	Untreated leukaemics <i>n</i> = 5	Significance *
Proerythroblasts	87.4 ± 8.1	61.0 ± 8.7	< 0.1
Macroblasts	74.9 ± 8.8	25.5 ± 6.0	< 0.005
Basophilic normoblasts	67.3 ± 3.3	28.0 ± 7.2	< 0.005
Polychromatic normoblasts	36.5 ± 6.5	8.0 ± 2.5	< 0.005
Orthochromatic normoblasts	0	0	—

* *P* values compared with normal persons.

The reduction of the mitotic indices of erythroblasts in untreated stem cell leukaemias was less marked than the reduction of the ³H-dThd labelling indices. It is improbable that this difference in reduction was caused by varying *in vitro* conditions because our *in vitro* results obtained on healthy subjects are comparable to those procured by other authors after *in vivo* labelling⁵. The difference between the reduction of the indices of the ³H-dThd labelling and the erythroblast divisions can be explained by assuming that mitosis is prolonged compared with the duration of DNA synthesis, which seemed to be comparable in normal and leukaemic erythroblasts. At least in the case of leukaemic blastocytes a prolongation of mitosis has previously been observed⁶ and has also been indirectly demonstrated using a method similar to ours¹.

On the average the ³H-dThd labelling indices of white cell precursors in untreated granulocytic stem cell leukaemia were also approximately one third of those of the controls (Table 1). This result agrees with those in other reports¹. In any single patient, the degree of the reduction of the labelling indices of the white cell precursors, when compared with those of the red cell precursors, was not closely correlated.

Our results confirm cytogenetic studies which indicate

the involvement of erythropoiesis in the "leukaemic degeneration"^{7,8}. The decreased proliferative activity of the erythroblasts⁹ may be a contributive cause of anaemia in this disease.

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the dried weight of the erythrocyte membrane preparation it can be calculated that at least two thirds of this protein must lie outside the lipid layer, perhaps to either side of it to form a sandwich structure of the type first suggested by Danielli and Davson⁴.

Penetration of the lipid layer by proteins may still be a very important feature from the point of view of the stability of membrane structure and of membrane function, but it may be looked on as a refinement of the lipoprotein sandwich model. So too with the observation that the protein configuration approximates that of a globular protein and the suggested possibility that the lipid may to some extent and under certain conditions adopt a configuration other than that of a continuous bilayer. All of these details can be incorporated without difficulty in this kind of model which was always intended simply to represent an average picture of a membrane.

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Competitive Hybridization with Brain RNA fails to confirm New RNA induced by Learning

MUCH circumstantial evidence implicates protein and RNA synthesis in memory consolidation and increasing interest in work directed toward elucidating the macromolecular chemical processes underlying learning^{1,2}. A derepression model has been advocated by Bonner³, who also suggested a method by which the model might be tested. Newly induced RNA molecules would be gene products, present in the brains of learning animals but not naive animals, and they should be able to be pulse labelled and detected by competitive hybridization experiments.

The "detection of RNA species unique to a behavioural task" by competitive hybridization has now been reported by Machlus and Gaito⁴⁻⁶. When 50 µg of DNA was hybridized first with 50 µg of unlabelled, naive brain RNA and then with 50 µg of labelled, learned brain RNA, there was about 50% competition. But when the DNA was hybridized first with unlabelled, learned RNA and then labelled, naive RNA, no radioactivity was observed; there was apparently 100% competition. This was taken as evidence that there were new species of RNA in the brains of the trained rats. Our data show no differences between the RNA from trained and naive rats. Control experiments and consideration of other data in the literature for hybridization with nucleic acids from higher organisms lead us to believe that the competition values reported by Machlus and Gaito are unrealistic and incorrect.

We have attempted to reproduce their results as follows: Sprague-Dawley male rats, 200-250 g, were injected intraventricularly with 40 µCi 5-³H-uridine in physiological saline or with physiological saline. Naive rats were returned to their home cages and killed 90 min after injection. Trained rats were put into a training apparatus 60 min after injection and allowed to become accustomed to the box for 15 min, and then were given 15 min of shock avoidance training, fifteen trials in 15 min. They learned the task well within four or

Lipid Layer in Cell Membranes

MEASUREMENTS of the extent of shrinkage of membranes which results from hydrolysis of phospholipid components by phospholipase C provide a direct indication of the area occupied by lipid in cell membranes. Maximum treatment of erythrocyte ghosts with phospholipase C (*Clostridium welchii*) liberates approximately 70% of the membrane phospholipid phosphorus and the surface area of the ghosts is decreased by 45-55% as calculated from diameter measurements made on spherical ghosts observed by phase contrast microscopy¹ and more recently from ghost volume measurements by an exclusion technique involving the use of ¹⁴C labelled sucrose. There is strong evidence that the phospholipid molecule as a whole is displaced from the membrane but the fate of the other membrane lipids is not established although it has been demonstrated that a residual lipoprotein structure persists. To indicate the quantitative significance of the observations, however, we have assumed that all lipids are removed in the same proportions as for the phospholipid. The observed shrinkage of the membrane by 50% would then be attributed to the loss of 70% of the membrane lipid. This would indicate that lipid occupies an area corresponding to $100 \times 50/70 = 70\%$ of the overall membrane area. Should any lipid be displaced to a lesser extent, then the figure for the area occupied by lipid would be increased to more than 70%.

An equivalent study² of muscle microsomes treated with phospholipase C demonstrated a shrinkage of 55% when 70% of the phospholipid of the membrane was hydrolysed. In this membrane phospholipid accounts for about 90% of the total lipid reported³ so that the extent of phospholipid hydrolysis gives a much more accurate indication of the probable extent of displacement of lipid from the membrane. The conclusion drawn from these experiments is that lipid occupies at least 80% of the area of the muscle microsomal membranes.

Thus in two experiments involving a surface membrane and a membrane preparation derived mainly from endoplasmic reticulum (membranes with significantly differing lipid compositions) there is direct evidence that interruption of the lipid layer by other components such as protein amounts certainly to no more than 30% and probably much less. Consequently, because protein accounts for about 60% of

Table 1 Hybridization Competition with Trained and Naive RNA

	Competitor RNA	Testor RNA	Competition +s.d. (%)
A	Naive	Naive	36.1 ± 3.1
B	Naive	Trained	32.7 ± 4.9
C	Trained	Trained	38.0 ± 2.3
D	Naive	Trained	35.8 ± 4.8

In the first experiment, A versus B, naive and trained RNA were compared as testor, and in the second experiment, C versus D, naive and trained RNA were compared as competitor. RNA was prepared separately from the brains of four rats for each type of RNA in each experiment. Each competition value was calculated from four independent determinations performed in duplicate. The specific activity of the labelled RNA was about 80 c.p.m./μg. Ribonuclease resistant hybrid RNA without competitor represented about 1.5% of the input label, or 60 c.p.m.

five trials. At the end of the training period the rats were killed immediately, and total RNA was prepared from whole brain by a hot phenol procedure. DNA prepared by the procedure of Marmur⁷ was denatured, immobilized on nitrocellulose membranes and hybridized in 1 ml. of 6×SSC at 66° C (ref. 8). Fifty μg of DNA was hybridized first with 50 μg of unlabelled competitor RNA for 12 h; then 50 μg of labelled testor RNA was added and the incubation was continued for 12 h. Adding the testor RNA to the vial after pre-incubation of the competitor RNA with the DNA should maximize the observed competition.

Two experiments (Table 1) were performed in conditions comparable with those described by Machlus and Gaito—the same amounts of DNA and RNA, the same incorporation time for the labelled RNA, the same temperature and time for annealing, and so forth. No statistically significant differences between trained and naive RNA were observed. All combinations of competitor and testor showed equal amounts of competition, about 36%. Small differences between trained and naive could go undetected, but these competition values are totally different from the 100% reported by Machlus and Gaito. Competitor RNA only partially blocked subsequent hybridization with testor RNA even when competitor and testor were identical, A and C.

A control experiment was performed in which 50 μg of DNA was hybridized for 12 h with increasing amounts of 90 min pulse labelled brain RNA. There was a nearly linear increase in the amount of hybridized RNA in the range between 50 μg and 200 μg of RNA, which demonstrates that 50 μg of this RNA does not saturate its complementary gene sites on 50 μg of DNA in these conditions. Without saturation of complementary gene sites we could not expect complete competition. A competition curve with 50 μg of DNA, 50 μg of testor RNA and increasing amounts of competitor RNA showed only about 50% competition with 200 μg of competitor RNA. These observations are consistent with numerous others in the literature which show that very large excesses of short-term pulse labelled RNA from higher organisms are required to approach saturation of complementary DNA gene sites^{9–11}, and very large amounts of competitor RNA are required for effective competition^{12,13}. Large amounts of competitor are especially important when the competition is accomplished by pre-incubation rather than simultaneous incubation^{14–16}.

The reason for the lack of efficient competition with nucleic acids from higher organisms seems to be that many of the RNA species synthesized in the cell are present in such low concentration that we cannot expect them to hybridize in the usual conditions¹⁷. Most of the hybridization usually observed probably represents reassociation of RNA with redundant genes¹⁸. In presaturation competition experiments, unless we use very large amounts of RNA, we can expect only a small fraction of the messenger RNA species to hybridize during the first incubation. During the second incubation, most sites coding for messenger RNA will still be free, so little competition will be observed.

Competitive hybridization now has considerable popularity

as a technique for demonstrating altered RNA metabolism in higher organisms, for example during embryonic development^{19,20}, during liver regeneration^{21,22}, in malignant versus normal cells^{23,24} and after hormone treatment^{13,22,25,26}. Unfortunately, much of this type of work is difficult to interpret reliably. Several points should be kept in mind. Generally the hybridization of RNA from single copy genes is not clearly distinguished from that of RNA which is the product of repetitive genes. Some messenger RNA molecules may be coded for by repetitive genes, but most are not²⁷. Hybridization in these systems is not stringently locus specific, and the amount of competition observed depends strongly on the ionic strength and the annealing temperature¹². Much, if not most, of the RNA synthesized in the cell turns over very rapidly and never leaves the nucleus²⁸, and after a short-term pulse, much of the label will be in this type of RNA which is not functioning as messenger RNA. Slight changes in precursor pools can thus cause different populations of RNA species to be labelled, and could lead to competitive hybridization data which might erroneously be interpreted as demonstrating induction of new species of RNA. This last consideration is especially important for evaluating future hybridization results relating learning and brain RNA metabolism, for it seems that with the training situations which produce an increase in the incorporation of RNA precursors there are also ill-defined, regional, transient changes in precursor pool concentrations^{29,30}. Nevertheless, the technique seems to be fairly sensitive, and in the proper conditions and with the proper controls it may well be capable of providing valuable information about brain function.

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Mitochondrial Changes in Preoptic Neurones after Capsaicin Desensitization of the Hypothalamic Thermodetectors in Rats

CAPSAICIN, the pungent principle in red pepper (paprika), is a potent irritant causing a sensation of burning pain. After initial violent stimulation, however, this substance induces a selective insensitivity to pain (desensitization) elicited by chemical agents^{1,2}. This long-lasting insensitivity is accompanied by ultrastructural changes in the mitochondria of one type of neurone in the spinal ganglia³.

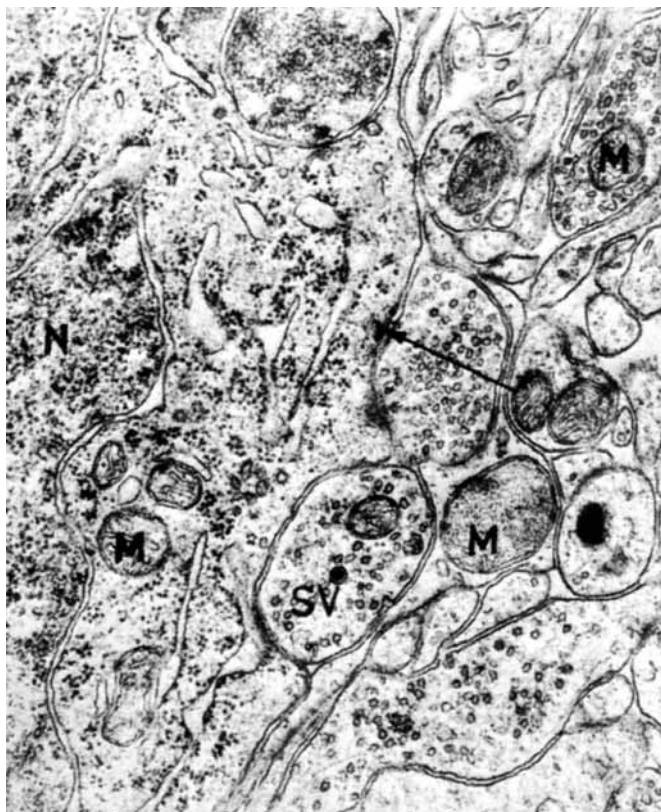


Fig. 1 Part of a "small" type nerve cell from the preoptic area of a control rat. The mitochondria of the nerve perikaryon do not differ from those of the neighbouring nerve and glial elements. The arrow indicates a site of axosomatic contact. N, Nucleus of the nerve cell; M, mitochondria; SV, synaptic vesicles. $\times 40,000$.

Recently it has been found that capsaicin also stimulates and subsequently desensitizes the hypothalamic warmth detectors^{4,5}. We have examined the submicroscopic structure of the preoptic area of the anterior hypothalamus, where—according to the physiological evidence—the hypothalamic warmth detectors are situated⁶. No morphological characteristics for the identification of these thermodetectors have hitherto been described.

For desensitization, rats weighing 140–180 g were treated with 15 mg or 15+20 mg of capsaicin, administered subcutaneously, on two consecutive days and killed 2 days, 10 days or 5 months after the last dose. Samples were removed after median section of the brain from the area just beneath the anterior commissure. They were fixed by perfusion with a buffered solution of paraformaldehyde–glutaraldehyde mixture according to Karnovsky⁷; or in buffered osmic acid, according to Millonig⁸. After gradual dehydration with ethanol, the tissue pieces were embedded in 'Durcupan' (Fluka). Thin sections for electron microscopic examination were made from selected blocks containing the clearly visible bundles of the anterior commissure. This was controlled in semi-thin sections

under the light microscope. The ultrathin sections were made by means of a Porter–Blum ultramicrotome, stained with lead citrate according to Reynolds⁹; and were investigated on a Tesla 242 D table electron microscope.

In the area of the hypothalamus two types of nerve cells have been described¹⁰. They are easily recognizable by means of electron microscopy, and are identified as nerve cells by their axosomatic synapses. In control rats no special structural difference or swelling of the mitochondria was seen in either of these cell types. The shape and size of the mitochondria did not differ from those seen in the neighbouring glial, axonal or dendritic elements. In rats desensitized by capsaicin in one of these cell types, a characteristic swelling of the mitochondria was observed, without any alteration of the mitochondrial structure of other nervous or glial elements. This cell type is characterized by its smaller size, a thinner cytoplasm containing rough endoplasmic reticulum rather than free ribosomes (Fig. 1). (The precise description and characterization of the cellular elements of the investigated area will be published elsewhere.) Fig. 2 shows the same type of cell in a rat pre-treated with 15 mg capsaicin 10 days before the experiment. The mitochondria are impaired only in the perikaryon: they are swollen, their matrix is less electron dense, and the cristae are irregular; but the space between their outer and inner limiting membranes is not increased. The impairment of the perikaryal mitochondria can be demonstrated even 5 months after the capsaicin pre-treatment (Fig. 3). This illustration also shows that the neighbouring glial and neural elements do not contain impaired mitochondria.

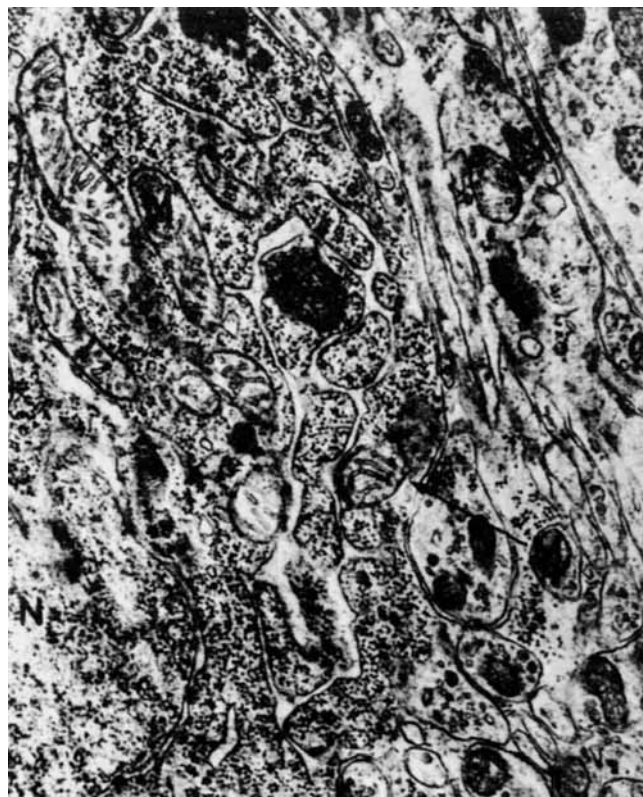


Fig. 2 The same type of nerve cell as in Fig. 1, from a rat 10 days after pre-treatment with 15 mg capsaicin. Swollen mitochondria can be observed only in the perikaryon. The arrow indicates an axosomatic synapse. N, Nucleus of the nerve cell; M, mitochondria. $\times 28,000$.

The mitochondrial alterations in the perikarya of neurones of the preoptic area were similar to those found in sensory neurones of the spinal ganglia of capsaicin-desensitized rats. In both cases the alterations were surprisingly long-lasting and were restricted to one type of neurone³. The warmth detectors in the preoptic area, like the peripheral chemo-

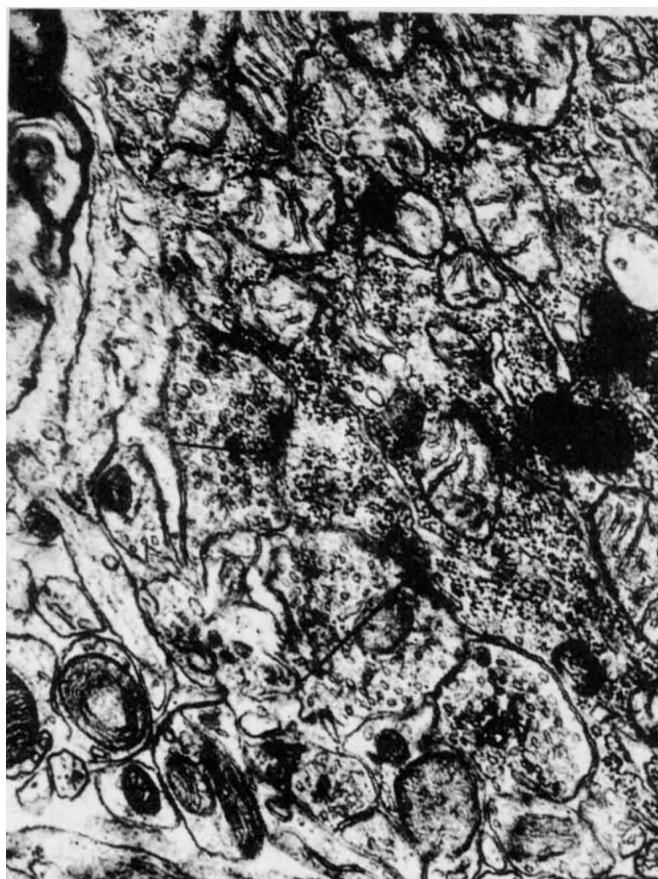


Fig. 3 The small type of nerve cell in a rat investigated 5 months after pre-treatment with 15 mg capsaicin. Note the severe damage to the perikaryal mitochondria. The arrows indicate axosomatic synapses. M, Mitochondria; SV, synaptic vesicles. $\times 38,000$.

sensitive pain receptors and possibly the temperature receptors, can be rendered insensitive for a long time by pre-treatment with capsaicin^{1,2}. The correlation between the electron microscopical changes and functional disturbances in capsaicin-desensitized rats is obvious; we therefore conclude that the nerve cells with the impaired mitochondria are warmth detector neurones.

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The *in vivo* Effects of Semipermeable Microcapsules containing L-Asparaginase on 6C3HED Lymphosarcoma

SEMI-PERMEABLE microcapsules are spherical ultrathin polymer membranes of cellular dimensions each enveloping a microdroplet of protein solution or suspension^{1,2}. Microencapsulated enzymes, while prevented from leaking out to give rise to hypersensitivity or immunological reactions, can act on external substrates dialysing across the semipermeable membranes^{3,4}. Microencapsulated enzymes include those present in erythrocyte haemolysates, urease, catalase, trypsin, uricase and L-asparaginase^{1,4}. L-Asparaginase suppresses the growth of certain asparagine dependent tumours⁵ by depleting the extracellular supply of asparagine. Recent reviews⁶⁻⁹ suggest that parenterally injected *Escherichia coli* asparaginase is removed rapidly as foreign protein and that there appears to be a relationship between the antitumour activity and the plasma half-life of L-asparaginase. In addition, *E. coli* asparaginase may give rise to hypersensitivity and immunological reactions. Because microencapsulated L-asparaginase acts efficiently *in vitro* and *in vivo* on asparagine which dialyses across the microcapsule membranes¹⁰, we have examined the effects of microencapsulated asparaginase on 6C3HED lymphosarcoma cells implanted in mice.

L-Asparaginase (Worthington or Sigma) was microencapsulated by a modification of the standard procedure^{1,2}. 1,260 units of the enzyme were dissolved in 1.5 ml. of a 10% haemoglobin solution. An equal volume of a freshly prepared alkaline 1,6-hexamethylenediamine solution (as aqueous solution containing 4.4 g% 1,6-hexamethylenediamine (Eastman), 1.6 g% sodium bicarbonate and 6.6 g% sodium carbonate) was then added. Immediately after mixing the two solutions, the following steps were carried out: 15 ml. of a "mixed solvent" (chloroform-cyclohexane, 1:4, containing 1% span 85 (Atlas Powder Co)) was added to the aqueous solution; the mixture was emulsified mechanically for 1 min at 4° C using a 'Jumbo' magnetic stirrer (Fisher) at speed "5" to give emulsified microdroplets of 80 μ m mean diameters. 15 ml. of 0.018 M Sebacyl chloride solution—prepared immediately before use by adding 0.1 ml. of pure Sebacyl chloride (Eastman) to 25 ml. of the 'mixed solvent'—was added. After 3 min at the same stirring speed, the reaction was quenched by the addition of 30 ml. of the "mixed solvent". All the supernatant was removed by centrifugation or sedimentation and 30 ml. of a dispersing solution (equal volumes of 'Tween 20' and water) were added. The suspension was stirred at a speed "8" for 1 min. The speed was then decreased to "5" and 50 ml. of water was added to the stirred suspension. The suspension was stirred for another 30 s and then poured into a beaker containing 200 ml. of saline. After removal of the supernatant, the semipermeable microcapsules were washed repeatedly in saline to remove 'Tween 20' and any microcapsules which were not well formed. Only properly prepared microcapsules which did not show any leakage of enzymes were used in the experiments. Control microcapsules were prepared in exactly the same way, except that asparaginase was not added to the haemoglobin solution.

In vitro studies showed that ¹⁴C-labelled asparagine equilibrated rapidly across the microcapsule membranes (unpublished data of S. Chan, B. Lesser and T. M. S. C.). When assayed by the ammonia procedure¹¹ the enzyme activity of microencapsulated asparaginase was 70 units ml.⁻¹ of a 50% microcapsule suspension. Asparaginase, whether in free solution or in the microencapsulated form, had the same K_m values but the microencapsulated enzyme had a lower V_{max} value (unpublished data). The microencapsulated asparaginase in aqueous suspension retained 80% of its original activity after 3 weeks of storage at 4° C.

In the *in vivo* experiments, 6C3HED lymphosarcoma cells were injected into C3HHeJ mice (Jackson Laboratories, Bar Harbor). The procedure¹¹ was modified slightly by using ten times the usual number of cells: each mouse received a subcutaneous injection of 500,000 6C3HED lymphosarcoma cells in the groin. Immediately after implantation, each mouse was given one of the following intraperitoneal injections: 0.05 ml. g⁻¹ body weight of saline; 0.05 ml. g⁻¹ body weight of a 50% suspension of control microcapsules; 0.05 ml. g⁻¹ body weight of an asparaginase solution (70 units ml.⁻¹ solution); or 0.05 ml. g⁻¹ body weight of a 50% suspension of microcapsules containing asparaginase (with an activity of 70 units ml.⁻¹ 50% suspension). The behaviour of the implanted tumours was observed as described¹¹. Table 1 shows the time when the tumours first appeared. The results show that in comparison with the asparaginase solution, the microencapsulated form is much more effective in suppressing the growth of implanted mouse lymphosarcoma. In order to explain this difference, one might look at a separate series of earlier experiments in which nylon microcapsules of 80 µm mean diameter containing ⁵¹Cr-labelled heterogenous haemoglobin were injected intraperitoneally. After the first week, the microcapsules were well dispersed over the whole peritoneal cavity. After the second week they were found in larger numbers in the upper parts of the peritoneal cavities. No significant radioactivity was detected in the lung, liver, spleen, lymph nodes, blood or particle free peritoneal washings. Recovered radioactivity was associated with the microcapsules in the peritoneal cavity for 4 weeks. Thus, intraperitoneally injected microcapsules of 80 µm mean diameter remained in the peritoneal cavity for at least 4 weeks and the microencapsulated haemoglobin did not leak out of the microcapsules throughout this time. These results seem to support the possibility that after parenteral injection, free asparaginase is removed rapidly as foreign proteins^{7,8}, whereas the microencapsulated form remained inside the microcapsules in the peritoneal cavity. In this way, asparaginase could continue to act on asparagine dialysing into the microcapsules.

Table 1 Time (Days) Implanted Lymphosarcoma First Appeared

	Saline	Control microcapsules	L-Asparaginase solution	L-Asparaginase microcapsules
	8	7	10	19
	8	7	10	19
	8	7	10	19
	8	8	10	20
	9	8	11	20
	9	8	11	20
	10	10	13	>120
	10	10	14	>120
	10	10	18	>120
	10	10	20	>120
	10	10	21	>120
	10	10	21	>120
Mean ± s.d.	9.0 ± 0.9	8.7 ± 1.6	14.0 ± 4.5	> 69

Microcapsules with biologically compatible membranes have been prepared¹⁰. Insoluble enzymes like urease and trypsin have also been microencapsulated in this laboratory. Such progress may eventually lead to preparations which might act indefinitely after parenteral injections. Moreover, this approach¹² or modifications^{13,14} of it need not be confined to the examples mentioned; there are other amino-acid dependent tumours—for example, serine dependent leukaemia¹⁵. It may also lead to methods of replacing deficient enzymes in cases of inborn errors of metabolism¹⁶ and of removing uremic metabolites^{12,17–20}.

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Selective Neurone Death as a Possible Memory Mechanism

It is a widely deplored fact that every day many thousands of our brain cells die and, unlike other types of cell, are never replaced^{1,2}. I suggest that this may not be a purely destructive process, as is normally supposed, but may represent a mechanism for one of the brain's most constructive functions, memory or information storage.

One naturally thinks that the loss of elements from a system must lead to its degradation, but this is not necessarily so if the elimination is non-random³. A sculptor changes a homogeneous lump of rock into a complex statue by subtraction, not addition, of material. An electronic data processing machine is most likely to be made by connecting components up in complex ways, and then enriching the connexions to make it even more complex. On the other hand, it could be constructed by starting with extremely rich, even random interconnexions, and then carving out a more meaningful organization by selectively cutting wires.

I propose that selective neurone death may be a mechanism of information storage in the brain. The parallel between learning and evolution would thus be even closer than has hitherto been suggested⁴. In both cases non-random death would be the mechanism of increase in complexity and adaptiveness.

I shall not suggest details, or give evidence for this idea, but simply point out that it is a plausible possibility which deserves to be considered alongside other vague theories with no supporting evidence. Testing the theory might require comparison of neurone numbers in animals given different amounts of training, or subjected to environments of differing richness. Incidentally, rats reared in an enriched environment have been found to possess fewer neurones in the field examined (part of

the visual cortex) than rats reared in an impoverished environment⁵. The authors suggested that the apparent decrease in cell numbers could be accounted for by an increase in the volume of brain tissue which the same number of neurones were occupying. It remains possible, however, that at least part of the difference in cell density was a consequence of a real difference in cell numbers.

The same authors⁶ found that an enriched environment increased the numbers of cortical glial cells, and list some possible explanations of this fact. My theory adds one more. The glia may be the agents of selective death among the neurones, and might therefore be expected to be more numerous in animals storing large quantities of information. It is already known that one of the main causes of neurone death in mice and men is neuronophagia—the neurones are engulfed and devoured by glia^{7,8}. An important selection pressure acting on cortical neurones may therefore be predation.

The possible involvement of glia is not, of course, an integral part of the theory. Disuse may be a more plausible principal cause of neurone death. This is the inverse of the idea, common to many neuronal theories of learning, that pathways which are most commonly used become facilitated.

The theory proposed here may seem fanciful at first. Further reflexion shows, however, that its lack of verisimilitude is mainly a consequence of the highly improbable postulate on which it rests; namely, that brain cells are decreasing in numbers at a prodigious rate daily. Because this postulate, however far-fetched, is an established fact, the present theory is not suggesting anything very implausible in addition; rather the reverse, as it makes the process seem less wasteful. All that is at issue is whether neurones die at random, or selectively, in such a way as to store information. Students of evolutionary theory will be sceptical, to say the least, of the idea that 100,000 deaths per day could be functionally completely random.

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Demonstration and Implications of Lysozyme and Immunoglobulins in Human Ear Wax

HUMAN cerumen (ear wax) occurs in two phenotypic forms, wet and dry, believed to be controlled by a single pair of genes in which the wet allele is dominant over the dry. Mongoloid peoples, including American Indians, characteristically have high frequencies of the dry allele, whereas among Caucasians and Negroes the wet allele predominates¹⁻³. Although no reason for this genetic dimorphism has been found^{4,5}, the extreme variations in frequencies of the two alleles among human populations suggest some adaptive value, possibly with respect to disease resistance. In this study, dry and wet cerumen was examined for the presence of lysozyme and immunoglobulins which are known to be present in nasal

secretions, tears, saliva, and to play a role in resistance to infection⁶⁻⁸.

Samples of cerumen were obtained by curette from 588 normal Caucasians, Chinese and Negroes with clinically normal external ear canals, and were classified as wet (sticky) or dry according to the criteria of Matsunaga¹. They were then weighed and suspended in 0.1 ml. of 'Triton × 100' diluted 1 : 10 with distilled water, sonicated for 30 min, and mixed thoroughly on a vortex mixer. The lysozyme assay was adapted from that described by Osserman *et al.*⁹. Heat-killed *M. lysodeikticus* organisms were suspended in small amounts of phosphate buffered agarose poured into Petri plates. The prepared cerumen samples were placed in wells cut in the agar. Standard dilutions of purified egg white CP-lysozyme controls were run with each Petri plate. The plates were left in a moist chamber at room temperature (24–26° C) for 24–36 h. Zones of clearing developed in the initially translucent gel as the result of bacterial lysis by lysozyme.

Antibody studies were made using immunodiffusion techniques¹⁰ set up with cerumen suspensions and with IgA and IgG antibody. The IgA or IgG antibody was then placed in the centre well; diffusion was allowed to take place at room temperature in a moist chamber for 3–4 days, and precipitin lines were recorded. Anti-human lysozyme antibody (provided by Dr Elliott Osserman, Columbia University School of Medicine) was reacted in lysoplates against cerumen samples to determine whether the lysozyme present was of human origin. Egg white lysozyme was used as a control. Lysozyme activity was present in 242 of the 588 samples (41.1%), and seemed to be related to the phenotype of the cerumen. Lysozyme was found in 84.6% of the samples of the dry type and in only 31.4% of the wet type.

When grouped according to the racial background of the subjects, the results indicate that although lysozyme was present in most subjects with the dry type ear wax, there were distinct differences in the frequency of the enzyme positive reaction in wet cerumen among the racial groups (Table 1). These were: Negro 45.1% positive, Caucasian 32.5% positive, and Chinese 18.6% positive. These differences were statistically significant ($P < 0.01$ – 0.001 , 2 d.f.). In a subsample of 74 wet and 10 dry specimens, immunoprecipitin tests revealed IgG antibody in all ten dry cerumens, and both IgG and IgA antibody in one wet type. Attempts to demonstrate the presence of inhibitors of lysozyme activity in cerumen samples absent in enzyme activity with this assay were negative.

Table 1 Frequency of Occurrence of Lysozyme in Wet and Dry Cerumen among Caucasians, Chinese and Negroes

Groups	Cerumen type		Lysozyme present	
			No.	(%)
Caucasians	Wet	(363)	118	32.5
	Dry	(5)	5	100.0
Chinese	Wet	(70)	13	18.6
	Dry	(99)	83	83.8
Negroes	Wet	(51)	23	45.1
	Dry	(0)	0	0

Numbers of subjects examined appear in parentheses.

The lysozyme present was human in origin, as shown by the reaction of lysozyme positive cerumen samples with antibody to human lysozyme. In these, a zone of inhibition was clearly evident as a flattening of the circumference of lysis, whereas the egg white lysozyme patterns were not inhibited by anti-human lysozyme. These findings show that cerumen has some potential for antimicrobial activity in terms of lysozyme and immunoglobulin content. The prominence of lysozyme and of IgG immunoglobulin in the dry type of cerumen is striking. The latter findings are surprising in view of the reported presence of IgA type immunoglobulins in respiratory secretions, saliva and tears. It is, however, difficult to reconcile our findings with previous studies¹¹ which indicated that bacteria and fungi

grew luxuriantly on cerumen. The resident flora of the external auditory canal is composed of non-pathogenic micrococci and corynebacteria, with a few transient potentially pathogenic bacteria. Moreover, lysozyme by itself is not effective against pathogenic organisms, although it has been reported¹² that it can become active against pathogenic bacteria in the presence of specific immunoglobulin.

Recently McCullough and Giles¹³ suggested that the anthropological variation in cerumen types might be related to relative humidity and its selective influence through different rates of external ear canal infection in the two types of cerumen, and that cerumen type might be associated with altered resistance to external otitis. This agrees with our findings of an antibacterial potential of dry cerumen. Severe complications are very rarely associated with external otitis¹⁴, however, but commonly follow otitis media, a significant medical problem in American Indians¹⁵. Studies by Gregg (personal communication) in Sioux Indians indicate no significant difference in the rate of external or middle ear infections associated with cerumen type. It is, however, also possible that the cerumen dimorphism is a manifestation of a pleiotropic gene which affects other systems of resistance to infection.

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Preparation of Biologically Active Plague Murine Toxins labelled with ⁷⁵Se-Methionine

ALTHOUGH the physiology and mechanism of action of the plague toxins have been investigated quite extensively, the target organ(s) is still unknown¹. *Pasteurella pestis* toxin does not remain in a free soluble form either after injection or after infection with a virulent strain. It cannot be detected in the plasma of moribund animals, although whole blood is toxic to mice 48 h after infection. Thus, the toxin may be bound to erythrocytes or other particulate matter (cell debris), which is phagocytosed by macrophages and removed from circulation.

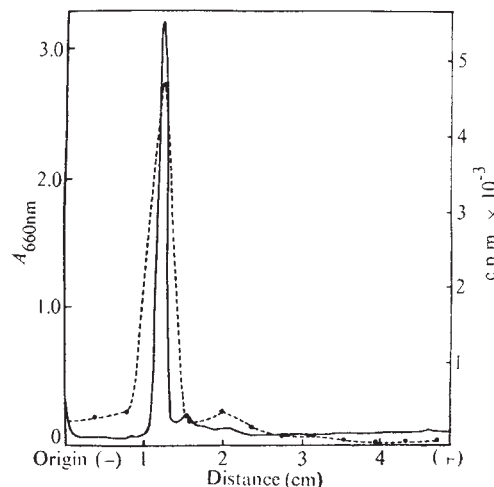


Fig. 1 Electrophoretic pattern of purified toxin A. —, Absorbance at 660 nm; ---, radioactivity (c.p.m.).

This could provide an efficient way of concentrating the toxin in specific organs such as the spleen or the liver, after breakdown of erythrocytes². If the spleen and liver are not the primary targets, the toxin could reach other organs through the circulation and exert its effect.

We have traced the fate of pure radioactively labelled toxin after injection into mice. A methodology for the isolation and purification of toxin labelled with ¹⁴C has been worked out in this laboratory (unpublished results of S. A. L.). The processing of samples for ¹⁴C counting, however, is quite laborious, and the quenching may lead to serious errors and misinterpretations. To simplify detection, toxin was labelled with a γ -emitting isotope (⁷⁵Se-methionine) which was included in the growth medium³.

The cells were grown for 12 h at 27° C and then 1 mCi of ⁷⁵Se-methionine (Squibb, 318 mCi/mg) was added. The culture was grown for a further 6 h until the maximum amount of toxin was available⁵. Cells were chilled and collected and the soluble protein fraction (post-ribosomal supernatant) was prepared. The toxic proteins, A (molecular weight 240,000) and B (molecular weight 120,000), were isolated by electrophoresis on polyacrylamide gel³. The fractions containing the toxins were macerated and extracted three times with two volumes of 0.01 M Tris chloride at pH 7.6. The extracts were lyophilized and dialysed against the same buffer.

Toxin preparations were analysed by disc gel electrophoresis⁶, with bromphenol blue indicating the migrating front. The gels were stained with 0.4% amido black in 7% acetic acid for 30 min and destained electrophoretically in methanol-acetic acid-water (27:7:66). The gels were then scanned with a Gilford spectrophotometer (model 2400) equipped with a linear transport attachment. The gel was then sliced in 5 mm sections, and the fractions were counted directly in a Baird-Atomic crystal scintillation counter.

As Fig. 1 shows, for both toxins A and B one protein band can be seen with an R (rate of migration relative to bromphenol blue) of 0.20 for A and 0.41 for B. The concentration of protein was determined by measuring the area under the toxin peak in the densitometric scan at 660 nm. Polyacrylamide gels were calibrated with different amounts of pure toxin (1–20 μ g per band) and a linear relationship was observed between the area and the amount of toxin in the band. For A the value of R was $102 \text{ mm}^2/\mu\text{g} \pm 5\%$ and for B it was $118 \text{ mm}^2/\mu\text{g} \pm 7\%$. The higher value for B was presumably due to the spreading of bands with materials that migrate further down the gel during electrophoresis⁷. Fig. 1 also shows that most of the radioactivity was associated with these proteins. The specific radioactivity of the preparations was calculated to be 300 c.p.m./ μ g for toxin A and 227 c.p.m./ μ g for toxin B.

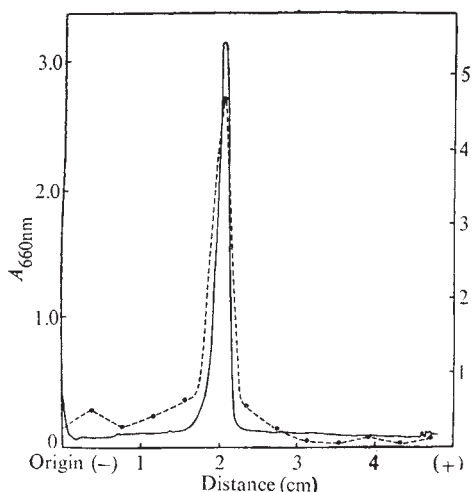


Fig. 2 Electrophoretic pattern of purified toxin B. —, Absorbance at 660 nm; ---, radioactivity (c.p.m.).

The toxicity of the isolated toxins was determined by injecting them intraperitoneally into Swiss albino mice as well as the inbred strains DBA-2 grey and C/57 black (Flow Laboratories, Rockville, Maryland). The LD₅₀ (24 h) was 1 µg for toxin A and 8 µg for toxin B⁸. We do not know whether the lower toxicity of B was a consequence of the substitution of sulphur in the methionine residues by selenium. If a methionine residue is in or close to the active site of the protein, this substitution could perhaps affect the biological activity. This question is under investigation (unpublished results of A. G. Lack.).

Diphtheria toxin¹⁰⁻¹² and botulinum toxin¹³ has already been labelled "externally" with either ¹²⁵I or ¹³¹I. But iodination of proteins is objectionable if the substitution in tyrosine alters the biochemical behaviour or the labelling is not homogeneous¹⁴. Furthermore, the distribution pattern in the animal may be misinterpreted because of de-iodination or re-incorporation¹⁵. The internal labelling which we have described should circumvent these obstacles. And it might provide a lead for the localization of the active site as illustrated by the different toxicity of the two proteins. We think that this method may be of general interest for the preparation of gamma-labelled radioactive protein with biological activity.

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Additive Edman Degradation to sequence Small Peptides

DURING the determination by Edman degradation of the amino-acid sequence of small peptides and the C-terminal region of longer peptides, extensive losses of material can occur when the 2-methylamino-5-thiazolinone obtained from the N-terminal amino-acid is extracted from the remaining peptide. This problem is encountered in degradations in which the thiohydantoin is identified directly as well as in the subtractive Edman degradation^{2,3}. In the latter procedure the amino-acids in the peptide are determined before and after removal of the N-terminal residue; the identity of the N-terminal amino-acid is established by difference. Because a separate peptide hydrolysis step and amino-acid analysis is required for each amino-acid in the sequence, the subtractive procedure is also relatively time consuming.

Recent studies⁴⁻⁶ have demonstrated the feasibility of analysing 3-methyl-2-thiohydantoin (MTH) and 3-phenyl-2-thiohydantoin (PTH) derivatives by gas-liquid chromatography (GLC). We have now developed an additive Edman degradation procedure for small peptides in which GLC of MTHs is used to identify the terminal amino-acid released at each step of the degradation. After one cycle of Edman degradation, an aliquot of the reaction mixture is removed and the MTH derived from the N-terminal amino-acid is identified by GLC. At each successive step of the degradation the MTHs produced in the prior steps appear on the chromatogram together with the newly released derivative.

Peptides of known sequence were obtained from Schwarz-Mann Laboratories, Orangeburg, New York. Three per cent OV-17 on 'Gas-Chrom Q' (100-120 mesh) column packing was obtained from Applied Science Laboratories, State College, Pennsylvania. All other reagents were redistilled before use as described previously⁴. The reactions were performed in 10×100 mm screw-capped tubes (teflon-lined caps) which had been treated with dimethyldichlorosilane to minimize adsorption of peptides and thiohydantoin to the glass.

The peptide to be sequenced (0.05-0.5 µmol) is dissolved in 200 µl. 50% aqueous pyridine and 1-2 µl. of triethylamine is added to bring the pH to 9.5-10.0 (determined with pH 9.0-13.0 indicator paper; Macherey, Nagel and Co., West Germany). To the peptide solution 5 µl. of methylisothiocyanate in 50 µl. of pyridine is added; an identical addition is made after 15 min. The mixture is flushed with nitrogen and held at 50° C for 30 min; after 0.5 h the solvents are evaporated under a stream of dry nitrogen at 50°. The residue is suspended in 0.2 ml. of ethyl acetate, which is then evaporated as above to ensure complete removal of the coupling solvents.

Anhydrous trifluoroacetic acid (200 µl.) is added to the methylthiocarbamyl peptide in the tube and the N-terminal amino-acid is split off and simultaneously cyclized to the thiazolinone by heating at 50° C for 10 min. After evaporation of the trifluoroacetic acid at 25° C under nitrogen, ethyl acetate is added to the tube and a portion of the solution is removed for conversion of the thiazolinone to the MTH derivative. This is accomplished by evaporation of the ethyl acetate at 25° C under nitrogen, addition of 200 µl. of 1 M HCl to the residue, and heating at 80° C for 10 min⁷. The peptide (minus one amino-acid) and most of the thiazolinone from the first cycle remain in the tube. This peptide is then subjected to successive cycles of Edman degradation as described above until the C-terminal acid is reached. Each cycle requires 50-60 min to complete.

The MTHs (except the histidine and lysine derivatives) are identified by GLC of their trimethylsilyl (TMSi) derivatives as previously reported⁴. The TMSi derivatives of the MTHs of histidine and lysine are unstable and give smaller peaks than anticipated when determined by GLC⁴. We have recently found that the acetyl derivatives of these two MTHs are stable

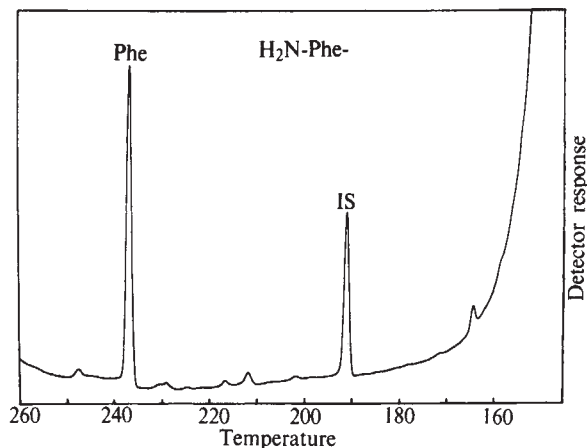


Fig. 1 Gas chromatogram of TMSi, MTH derivatives after one cycle of additive degradation of a pentapeptide. The amino-acid composition of the peptide is (Ala, Asp, Phe, Ser, Val). 2.5 nmol of internal standard (IS=TMSi, MTH-Leu) was injected at a sensitivity of 3×10^{-10} A for full scale deflection. Three minutes after injection of the sample, the column oven was programmed at $5^\circ/\text{min}$.

at 25°C for at least 2 days and upon GLC analysis give 3–4 times larger peaks than the corresponding TMSi derivatives. To form the acetyl derivatives the MTHs are dissolved in 100 μl . pyridine-acetic anhydride (1 : 1) and maintained at 25°C for 18 h; after dilution with 1 ml. of toluene the solution is evaporated to dryness at 80°C under nitrogen. The acetyl derivatives are dissolved in ethyl acetate and analysed on an OV-17 column. The oven temperature is programmed from 200°C to 260°C at $5^\circ/\text{min}$ and then held at 260°C for 10 min. The lysyl derivative eluted 14 min and the histidyl derivative 15 min after injection on the GLC column.

The sequence analysis by additive Edman degradation of the pentapeptide $\text{H}_2\text{N-Phe-Asp-Ala-Ser-Val-OH}$ is described in the following section. Initially, an amino-acid analysis of the peptide was performed by two different procedures. After acid hydrolysis, the amino-acids were analysed by the procedure of Roach and Gherke⁸ and as their MTH derivatives as previously reported⁴. These analyses confirmed that the peptide contained equimolar quantities of Ala, Asp, Phe, Ser and Val.

0.3 mg of peptide was sequenced by the additive procedure. After the first cycle of Edman degradation the mixture in the reaction vessel was dissolved in 0.5 ml. of ethyl acetate and 0.1 ml. of the solution was removed for conversion of the thiazolinone of the N-terminal amino-acid to its MTH deriva-

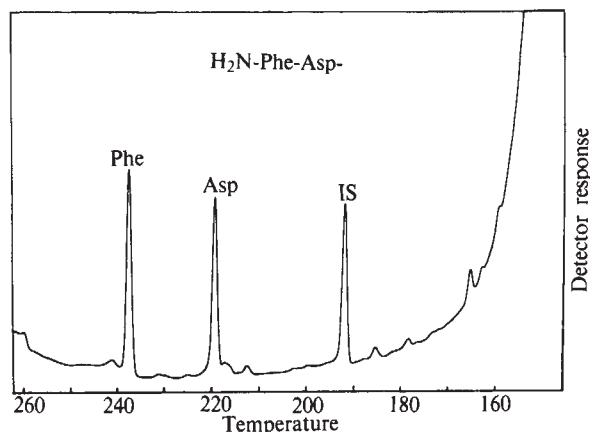


Fig. 2 Gas chromatogram of TMSi, MTH derivatives after two cycles of additive degradation of a pentapeptide. Conditions for analysis were the same as in Fig. 1.

tive. Before conversion of the MTH to its TMSi derivative 25 nmol of internal standard (MTH-leucine) was added, and the TMSi derivatives were analysed on an OV-17 column⁴. The chromatogram obtained (Fig. 1) shows that Phe is the N-terminal amino-acid of the peptide. From the relative detector response of equimolar amounts of TMSi, MTH-Phe and TMSi, MTH-Leu, the yield of TMSi, MTH-Phe as calculated from the chromatogram was 48 nmol.

After the second cycle of Edman degradation, 0.4 ml. of ethyl acetate was added to the reaction tube and 0.1 ml. of solution was removed for conversion of the thiazolinones to the MTH derivatives. Analysis of the TMSi, MTH derivatives by gas chromatography on an OV-17 column provided the chromatogram shown in Fig. 2, which demonstrates that aspartic acid is the amino-acid in the peptide adjacent to phenylalanine. The yield of TMSi₂, MTH-Asp was 48 nmol. Because 2-methylamino-4-phenyl thiazolinone was still present in the reaction mixture in addition to the peptide, this thiazolinone obtained from Asp. Thus, the MTH derived from it appears as the TMSi, MTH derivative in the chromatogram (Fig. 2).

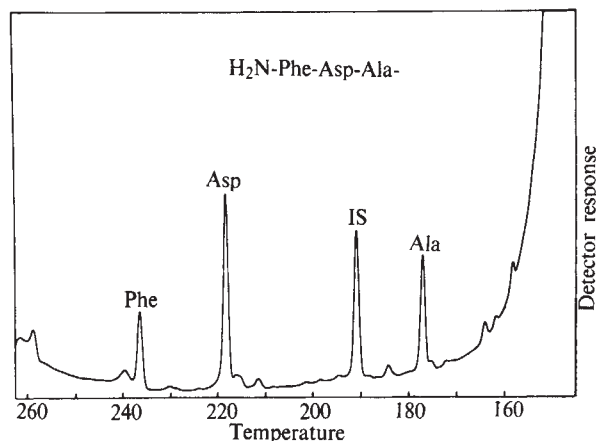


Fig. 3 Gas chromatogram of TMSi, MTH derivatives after three cycles of additive degradation of a pentapeptide. Conditions for the analysis were the same as in Fig. 1.

After another cycle of Edman degradation and conversion of 0.3 of the thiazolinones to the MTH derivatives, the chromatogram shown in Fig. 3 was obtained. The next amino-acid in the sequence is thus Ala. The yield of TMSi, MTH-Ala was 34 nmol, 71% of the yield of TMSi, MTH-Phe obtained after the first step of Edman degradation. The area of the phenylalanine peak relative to that of the internal standard is 75% less than the area of the phenylalanine peak in the first chromatogram. This decrease in peak size was observed with the other derivatives also and can be attributed to the instability of the thiazolinones in the reaction tube.

After four cycles of Edman degradation, the chromatogram shown in Fig. 4 was obtained, indicating that Ser is the next amino-acid in the sequence. The low yield of MTH-Ser, 15 nmol, is characteristic of this derivative.

With the sequence elucidated so far, and knowledge of the amino-acid composition of the peptide, one can predict that the C-terminal amino-acid is valine. This prediction was confirmed by a final cycle of Edman degradation (Fig. 5) in which 16 nmol of TMSi, MTH-Val was obtained. This represents 33% of the yield of the TMSi, MTH-Phe obtained in the first reaction cycle. Only 6 h were required to perform all the operations described.

To test the general applicability of the additive Edman degradation, several other peptides were sequenced (Table 1). During the sequencing of the peptide $\text{H}_2\text{N-Trp-Met-Asp-Phe-}$

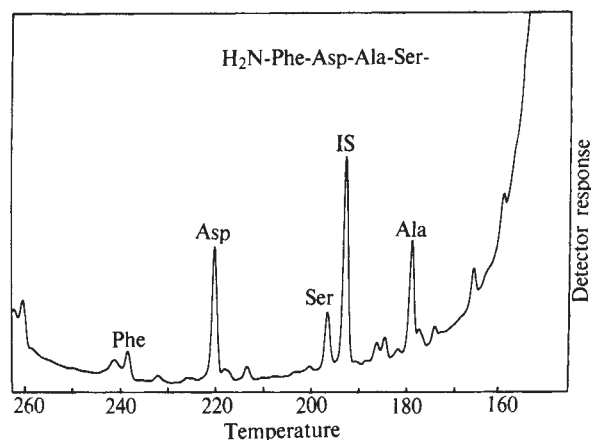


Fig. 4 Gas chromatogram of TMSi, MTH derivatives after four cycles of additive degradation of a pentapeptide. Conditions for the analysis were the same as in Fig. 1.

CONH₂ our previously described procedure had presented some difficulty⁴, presumably because of cyclization of aspartic acid². This problem was eliminated with the procedure outlined above, as were difficulties associated with extensive cyclization of glutamine residues. Peptides which contain more than one residue of the same amino-acid (for example, the hexapeptide containing three glycine and two proline residues shown in Table 1) can be sequenced with the aid of quantitative GLC. After each of the first three cycles of Edman degradation of the octapeptide shown in the table, the thiazolinones were completely extracted from the dried peptide with 0.2 ml. of ethyl acetate. The remaining pentapeptide was sequenced by the additive method.

Table 1 Peptides sequenced by the Additive Edman Degradation

H ₂ N- Leu- Trp- Met- OH
H ₂ N- Trp- Met- Asp- Phe- CONH ₂
H ₂ N- His- Ser- Gln- Gly- Thr- Phe ₂ OH
H ₂ N- Gly- Pro- Gly- Gly- Pro- Ala- OH
H ₂ N- Phe- Val- Gln- Trp- Leu- Met- Asn- Thr- OH*

* After each of the first three cycles of Edman degradation of the octapeptide, the thiazolinones were completely extracted from the dried peptide with 0.2 ml. of ethyl acetate. The remaining pentapeptide was sequenced by the additive method.

Using the method described, about 25 nmol per amino-acid (or 0.15 μ mol of hexapeptide) is required to sequence a peptide with 5 or 6 amino-acids. For analysis by GLC only 1–2 nmol of derivative is needed, however. It is conceivable that the

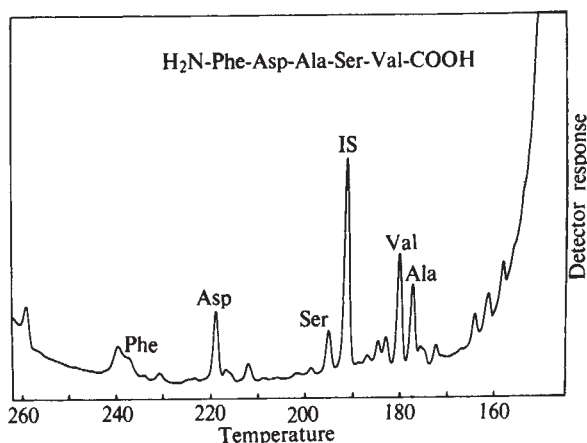


Fig. 5 Gas chromatogram of TMSi, MTH derivatives after five cycles of additive degradation of a pentapeptide. Conditions for the analysis were the same as in Fig. 1.

contaminating by-products seen as background in Fig. 5 could be reduced significantly by more careful purification of reagents and by use of an optimal quantity of methylisothiocyanate for quantitative reaction with the peptide. (The present procedure uses a large excess of this reagent.) With these refinements less peptide would be needed for analysis.

The results presented in this paper demonstrate the usefulness of the additive Edman degradation for sequencing small peptides and the C-terminal region of longer peptides. The method is fast and sensitive, and takes advantage of the inherent accuracy and reliability of gas chromatographic analysis. The procedure which has been described may provide a more practical and financially feasible approach to the elucidation of peptide sequences than other techniques currently being tested such as mass spectrometry⁹, automated solid phase degradations¹⁰ and analysis of peptides by a sequencer¹¹.

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Detection of Latent Fingerprints with ³⁵SO₂

GRANT *et al.*^{1–3} have reported that latent fingerprints on paper may be detected by autoradiography of the paper after it has been treated with ³⁵SO₂. Work carried out at the Health Physics and Medical Division, AERE, Harwell, has shown that a modified version of the technique of Grant *et al.* can be used to detect latent fingerprints on a wide range of papers. I have also found that the modified technique can be used to visualize latent fingerprints on finely woven fabrics.

I have investigated the compounds in the fingerprint deposits to which the SO₂ is bound by attempting to elute the ³⁵SO₂-treated deposits with a range of solvents. Almost all of the SO₂-labelled compounds were removed by elution with diethyl ether, suggesting that the labelled compounds are lipid. Myristic acid, palmitic acid, stearic acid, oleic acid and linoleic acid, which are the principal fatty acids of human depot fat⁴, were applied to filter paper and exposed to ³⁵SO₂ in the conditions used for latent fingerprint detection. Only the unsaturated acids, oleic acid and linoleic acid, were found by autoradiography to react with SO₂.

The addition of SO₂ to an olefine leads to the formation of the corresponding sulphone and frequently polymeric sulphones are formed. Attempts to separate the ³⁵S-labelled compounds in the ether extract of fingerprint deposits by thin-layer chromatography were unsuccessful. This was probably

because of the diverse nature of the fats and oils in human sweat and the consequent diverse nature of the reaction products with SO_2 .

Because the lipid constituents of human sweat are only very slightly water-soluble, the possibility of detecting latent fingerprints on papers that had been immersed in water was investigated. Preliminary results suggest that the modified technique of Grant *et al.* can result in a reaction between $^{35}\text{SO}_2$ and latent fingerprint deposits on paper that had been immersed in water for several hours.

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Distribution of Pethidine and Chlorpromazine in Maternal, Foetal and Neonatal Biological Fluids

EVIDENCE for placental transfer of drugs was obtained in 1885 when Preyer¹ observed mydriasis in newborns whose mothers had received belladonna during labour. Since then analgesia has been recognized as a considerable problem in obstetrics, for the opiates and other allied and synthetic narcotics administered during labour have respiratory depressant effects on the foetus. While the search for optimum analgesia with minimum adverse effects on the foetus continues, pethidine, first introduced in 1940², is still widely used—usually with other drugs. Comprehensive reviews of the literature^{3,7} relating to placental transfer of pethidine and its suitability for obstetrical use reveal wide discrepancies in clinical observations and a lack of precise experimental results. To provide quantitative data which may be correlated with systematic clinical observations, I examined the distribution of pethidine and chlorpromazine and a wide range of their metabolites in amniotic fluid, maternal and foetal plasma and maternal and neonatal urine.

Two hundred and twenty women received 50 mg–100 mg intramuscularly of pethidine, chlorpromazine or promazine, singly or in combination, shortly before delivery. Maternal, foetal and neonatal fluids were investigated for isolation, characterization and quantification of these drugs and their metabolites. Specimens were grouped according to "drug-delivery interval" (the time between administration of the drugs and delivery). All results were statistically evaluated.

Pethidine and norpethidine were found in the amniotic fluid and maternal and foetal plasma. Four additional metabolites—free and conjugated meperdinic acid and nor-meperdinic acid—were found in the maternal and neonatal urine. Chlorpromazine was found in the foetal plasma and chlorpromazine and 7-hydroxychlorpromazine in the maternal plasma: eight additional metabolites were found in the amniotic fluid. Chlorpromazine and twenty-five metabolites were isolated from the maternal urine and chlorpromazine and twenty-one metabolites from the neonatal urine (Table 1). Dihydroxy metabolites and chlorpromazine were found in amniotic fluid and in maternal and neonatal urine. Promazine was found to follow the same pattern of distribution as chlorpromazine.

Table 1 The Distribution of Chlorpromazine and its Metabolites in Amniotic Fluid and Maternal and Neonatal Urine

Chlorpromazine and metabolites	Amniotic fluid	Maternal urine	Neonatal urine
Chlorpromazine	+	+	+
Desdimethylchlorpromazine	+	+	+
Chlorpromazine sulphoxide	+	+	+
Desdimethylchlorpromazine sulphoxide	+	+	+
Desmethylchlorpromazine sulphoxide		+	+
Chlorpromazine N-oxide		+	+
7-Hydroxychlorpromazine		+	+
7-Hydroxychlorpromazine sulphoxide		+	+
7-Hydroxydesdimethylchlorpromazine		+	+
7-Methoxychlorpromazine		+	
7-Methoxychlorpromazine sulphoxide		+	
Conjugated :			
7-Hydroxychlorpromazine	+	+	+
7-Hydroxydesdimethylchlorpromazine	+	+	+
Chlorpromazine	+	+	+
7-Hydroxychlorpromazine sulphoxide	+	+	+
Chlorpromazine sulphoxide		+	+
7-Hydroxydesdimethylchlorpromazine sulphoxide		+	+
7-Hydroxychlorpromazine N-oxide		+	+
2-Chlorophenothiazine		+	+
2-Chlorophenothiazine sulphoxide		+	+
7-Hydroxydesmethylchlorpromazine sulphoxide		+	+
Desdimethylchlorpromazine sulphoxide		+	+
Desmethylchlorpromazine sulphoxide		+	+
7-Hydroxydesmethylchlorpromazine		+	+
Chlorpromazine N-oxide		+	
7-Methoxychlorpromazine sulphoxide		+	

+ = Present

To elucidate the origin of metabolites in the urine of the neonate, I investigated neonates from untreated mothers. These neonates received 1 mg doses of pethidine, chlorpromazine or promazine and their urines were examined.¹ It was clearly demonstrated that the newborn can metabolize drugs within 24 h after birth. Pethidine, norpethidine and meperdinic acid were isolated and chlorpromazine and six of its metabolites were obtained. These were free hydroxy and free and conjugated sulphides and sulphoxides, and free mono and dihydroxy derivatives. This shows that the neonate has a much greater ability to metabolize drugs than was believed; moreover, it increases substantially within the first 72 h after birth. A comparative study of the compounds found in the urine of untreated neonates from treated mothers with those found in urine of treated neonates from untreated mothers shows the presence of a number of conjugated metabolites in the former which do not appear in the latter. This finding is important because it extends knowledge of the foeto-maternal transport system; the extra compounds may be concluded to be of maternal origin and their appearance in urine of untreated neonates shows that the foeto-maternal system is permeable not only to the drugs but to many of their metabolites.

Brodie⁴ showed that drug-receptor interactions are generally in dynamic equilibrium with the level of free drug in plasma and that the concentration at the receptor governs intensity and duration of response. Although the concentration of drug in the plasma does not bear a direct relationship to the dose^{3,5} the mean plasma level can be related to overall response^{3,6}. These results for mean plasma levels³ substantiate the exten-

sive clinical observations of Shnider and Moya⁷ on neonatal depression. This investigation may therefore have direct therapeutic and toxicological implications for the clinician.

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Sensory Feedback in Regulation of Body Weight: is there a Ponderostat?

It has been postulated that "some correlate of body weight" might control daily food intake^{1,2}. This could work through sensory feedback, as in the case of behavioural temperature regulation. In thermal sensation a stimulus (limited to between 15° and 45° C) feels pleasant when it is conducive to homoeothermia and unpleasant when it threatens homoeothermia. This transformation of pleasantness is dependent not only on internal signals but also on the thermoregulatory set point³. The change of sensation from pleasant to unpleasant depending on the internal state also applies to taste and smell^{4,5}. We have explored this phenomenon further, to determine whether these changes in olfactory and gustatory sensations also were dependent on a set-point related to body weight. If modification of body weight also affects gustatory and olfactory sensation, this will provide strong evidence for (a) the existence of a regulatory process for body weight, and (b) the use of sensory feedback in feeding behaviour.

The subjects were three male adults (ourselves), apparently in good health, aged 35, 27, 50 yr. Each had been eating *ad lib.* with no attempt to control body weight, and had maintained his body weight approximately without change for at least 2 yr. For the first two trials (controls) body weights were 68, 76.5 and 90 kg respectively. After these control trials, each subject went on a reduced calorie diet of 500 to 800 kcalories/day with the aim of losing, respectively, 8%, 10% and 10% of body weight. Experimental trials were repeated (a) at half of the weight loss; (b) at the attainment of the minimum weight; (c) after 2 weeks and after 1 month of resting (taking 1,600 to 2,000 kcalories/day) at the lowest body weights; (d) after 2 days of overeating, that is, eating beyond subjective levels of satiety, to caloric levels of up to 8,000 kcalories/day*; and (e) after recovering the control body weight (two subjects), 4.5 months after the initial control period.

All tests were conducted before noon, the subject having had no food, drink or smoking before the test on the day of the test. Each test consisted of a series of tastes and smells

*Approximately 4,500 kcalories were ingested by each subject during the first lunch breaking the "fast". On this day, one of the subjects consumed 7,945 kcalories as opposed to his maintenance diet of 1,570 kcalories/day and to his weight-loss diet of 850 kcalories/day.

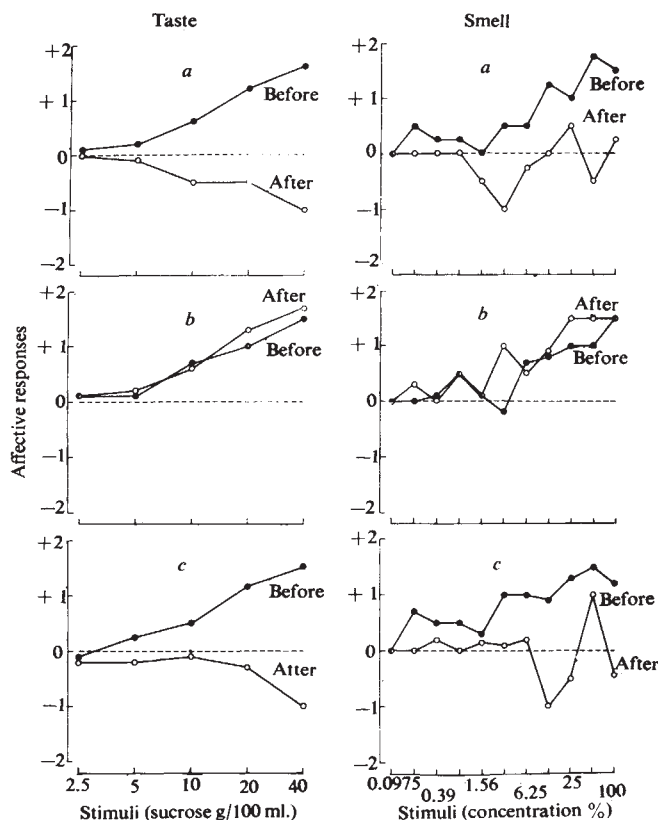


Fig. 1 Subjective evaluation of the pleasantness or unpleasantness of the taste and smell of sweet solutions. The responses shown represent typical results and are not the extremes obtained. a, Control: the filled circles (left) represent the evaluation, by one subject (M. C.), of the pleasantness (0 to +2) or the unpleasantness (0 to -2), on an infinite scale, of aqueous sucrose solutions, before glucose ingestion, on an empty stomach. The open circles represent the responses to the same concentrations, 1 h after ingestion of 50 g glucose dissolved in 200 ml. of tap water. Body weight "normal". On the right, the responses of another subject (R. D.) to the odour of various dilutions of concentrated orange syrup before (●) and after (○) stomach load of 50 g glucose in 200 ml. water. Body weight "normal". b, Experimental: "before" and "after" responses of the same subjects to the same solutions, but at a later date, after losing respectively 5.2 kg and 3 kg of body weight. c, Return to control level: responses of the same subjects after returning to their initial body weights, 4.5 months after the first controls.

presented to the subjects in random orders of concentration, before and after a glucose load taken by mouth. The five solutions for taste were respectively 10.0, 5.0, 2.5, 1.3 and 0.6 g of sucrose in 25 ml. of water. The eleven solutions for smell were: fully concentrated orange syrup ("Sirop Orange Concentre", made by Teisseire, Grenoble, and containing orange concentrate and sugar), then diluted in half, and then in half again, and so forth, so that the least concentrated was 0.00097 of the original in aqueous solution, all made up to the same volume. The subject was required to rinse his mouth, with tap water, always at the same temperature, at least three times at the start of the test, and after each solution tasted. For each taste the subject put the test solution in his mouth, without swallowing, and expectorated it after 15 s. He was immediately asked to give the solution a numerical rating, on a continuous scale, ranging from +2 ("very pleasant") to -2 ("very unpleasant"). 60 s after the end of rinsing, he was given another solution to taste, and so on, until all five were rated. Following the taste sequence, he was asked to close his eyes; a cup containing one of the orange scent solutions was placed under his nose, in contact with his nostrils, and he was allowed 3 s to sniff the odour. The cup was then removed and he was asked to rate immediately this odour on the same (+2 to -2) pleasantness-unpleasantness scale. This

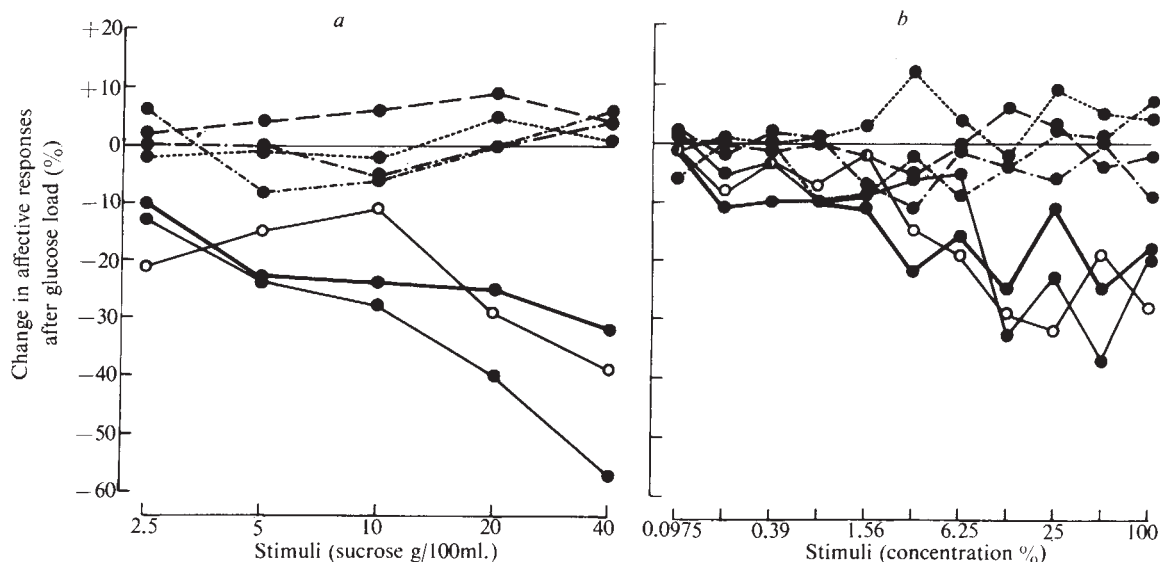


Fig. 2 Averages of all three subjects in terms of percentage changes after glucose ingestion. *a*, Percentage changes in subjective evaluation of pleasantness of the tastes of sucrose solutions of various concentrations, 1 h after the ingestion of 50 g glucose dissolved in 200 ml. of tap water, as compared with evaluation of same test solutions before ingestion of glucose. Total scale of -2 to +2 is set equal to 100%. *b*, Percentage changes in the subjective evaluation of pleasantness of the odours of concentrated orange syrup in various dilutions, 1 h after the ingestion of 50 g glucose dissolved in 200 ml. of tap water. ●—●, First control: "normal" body weight. Taste $P \ll 0.01$; smell $P \ll 0.01$. ●—●, Second control: "normal" body weight. Taste $P \ll 0.01$; smell $P \ll 0.01$. ●—●, Half way down in body weight loss (food intake 800 to 1,000 kcalories/day). Taste $P > 0.05$; smell $P > 0.05$. ●—●, First day at lowest body weight. Taste $P > 0.05$; smell $P > 0.05$. ●—●, After 2 weeks at lowest body weight (food intake 1,600 to 2,000 kcalories/day). Taste $0.05 > P > 0.02$; smell $P > 0.05$. ●—●, Two to four days after increase in body weight, with all subjects overeating (up to 8,000 kcalories/day). Taste $P > 0.05$; smell $P < 0.01$. ○—○, 4.5 months after first controls: return to initial body weight (two subjects). Taste $P \ll 0.01$; smell $P \ll 0.01$.

process was repeated at 1 min intervals until the series of eleven concentrations had been rated. Occasionally these series were repeated immediately in different order of presentation, to test the reproducibility of the subjective responses. No significant variability was found in such repeated trials. Following the olfaction tests, the subject drank 200 ml. of an aqueous solution containing 50 g of glucose. 1 h after the ingestion, the series of tastes and smells were repeated exactly as above, in the same sequence as before the glucose load. Each subject (as experimenter) was permitted to know the results of only one other subject's trials, and no results were compared until the end of each phase of the experiments.

Daily records were kept of each subject's body weight and total food intake in calories. Body weight was always measured on the same balance, with the subject nude, bowels and bladder voided. Foods and drinks were weighed and caloric values estimated from reference tables. Precision for weights is estimated at ± 0.01 and for caloric intake ± 0.05 .

The results for all three subjects are shown (Fig. 2) as percentage changes in affective responses after the glucose ingestion. For each subject, the response to each concentration of glucose, before the stomach load, was equated to 0%, and the change from this value measured on the scale of possibilities from -2 to +2. Thus, the total range of -2 to +2 = 100%. The same scale was used for olfactory responses. It is evident that during the control periods there was a highly significant decrease ($P < 0.001$; Wilcoxon signed rank test⁶) for each subject (for example, Fig. 1*a* and Fig. 2, solid lines) in the pleasantness of both the taste and the odour of sweet substances after glucose load, thus confirming our previous observations⁴. But starting with the first trials after the partial loss of body weight and continuing through all subsequent trials, at the lowest body weight, at 2 weeks after and 1 month after reaching the bottom weight, and shortly after having begun again to gain weight, no subject in any trial showed any significant decrease⁵ in his affective taste response after stomach glucose loading (Fig. 1*b* and Fig. 2). Not until the fourth experimental trial was there a significant change in the olfactory affective response.

After returning to their initial body weight, two subjects gave responses almost identical to those at the beginning of the experiment (Fig. 1*c*, Fig. 2). The third subject has not yet returned to his control body weight. The results therefore support the working hypothesis, and it seems possible to conclude that there exists in the body weight control system a biological "ponderostat", and that at least two of the pathways of action of this system are sensory. The pleasantness-unpleasantness of alimentary perceptions therefore depends more or less directly on a certain body weight set point. It is easy to see how pleasantness-unpleasantness can give rise to corrective alimentary behaviour. A possible objection to these experiments is that subjects were not naive. We have, however, partially confirmed our results by testing three naive subjects at various stages of body weights; there was no exception to the tendencies described here, but there were not enough observations for statistical analysis. Our own procedure, with ourselves as subjects, was partially blind and we often found that the recorded results were different from those which our subjective impressions had led us to expect. We found no significant difference when a series of tastes or odours was presented for a second time, the same day, in a different order, to the same subject. The concept of a ponderostat implies two internal signals. One, long or middle range, is the difference between the set value and the actual body weight. The nature of this signal is not known although the lipostatic theory recently has been re-emphasized⁷. The second internal signal, initiated by the ingestion of food, is a short-term "satiety" signal^{4,5}. From previous results and other workers' data^{4,5,8}, it is probable that the change in affective response was not the result of changes in either blood glucose levels, or of arterial-venous differences in glucose levels. An apparent paradox seen in these experiments was that non-obese subjects became psychologically "obese" when they became underweight: their affective responses to taste and smell became identical to those of obese subjects on limited food intake⁹. Obesity could be a resetting of the ponderostat at a higher value. Being beneath his set point, the obese subject will be unaware of some internal signals for satiety, and will give the same response as did our

subjects herein reported after body weight loss. If the obese human eats *ad libitum* he will presumably reach his regulated value and give a normal response⁹. Anorexia nervosa may be a resetting of the ponderostat at a lower value.

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Reversible Mechanochemical Cycle in the Contraction of *Vorticella*

The ciliate *Vorticella* has a stalk which is capable of coiling into a helix. The coiling is produced by the contraction of an intracytoplasmic thread, the spasmoneme, within a cylindrical sheath. Hoffmann-Berling¹ observed that the stalks of glycerinated preparations coiled in the presence of calcium ions and uncoiled when calcium was subsequently removed by the addition of ethylene diamine tetraacetate (EDTA), and that many cycles of contraction and relaxation could be produced by repeating this procedure, without adding adenosine triphosphate (ATP). He also found that contraction was not abolished by ATPase inhibitors. Townes and Brown², however, were later unable to obtain reversible contractions. The behaviour of glycerinated preparations was therefore investigated under precisely defined conditions.

When preparations made by glycerinating for up to 1 month in 50% glycerol, 0.1 M KCl, 10 mM histidine and 4 mM Na₂EDTA were treated with a medium containing 0.1 M KCl and 10 mM histidine with an EGTA/CaEGTA buffer of total concentration 8 mM at pH 7.0 the stalks remained extended if the calcium ion concentration was less than 10⁻⁷ g ions/l. As the calcium level increased progressively a point was reached at which coiling took place, and the stalks then remained coiled indefinitely unless the calcium level was lowered. The threshold level varied little when the preparations were left overnight in the calcium-buffered solution (Table 1).

Table 1 Average Threshold Calcium Levels

Time after removal from glycerol	pH	Temperature (°C)	Ca ²⁺ threshold (g ions/l.)
55 min	6.86	22	(4.21 ± 0.1) × 10 ⁻⁷
14 h 20 min	6.95	21	(5.65 ± 0.1) × 10 ⁻⁷

Average threshold levels of calcium measured with the same group of twenty preparations of *Vorticella convallaria*. The group was left overnight at room temperature in the reactivation medium between the measurements.

10 mM MgCl₂ had no effect on the threshold level of calcium, and the same threshold was obtained with an EDTA buffer. It was concluded that magnesium played no part in this type of contraction.

Extension and contraction were induced 35 times by treating stalks alternately with solutions containing 10⁻⁸ and 10⁻⁶ g ions Ca/l. The response could be elicited after several days at room temperature, even in the presence of the following inhibitors: 2 mM 'Salyrgan' (2-hydroxymercuric methoxypropylcarbonyl sodium acetate), 1 mM KCN, 2 mM dinitrophenol and 0.5 mM 2,4-dinitro-1-fluorobenzene.

In calcium-buffered media, ATP and MgCl₂ had no visible effect on the coiling or the threshold. If 0.1 mM CaCl₂ was added instead of the calcium buffer a minority of stalks became coiled. The further addition of 2 mM ATP and 4 mM MgCl₂ produced in some a tighter coiling, while others relaxed and pulsed, as previously observed by Hoffmann-Berling. These observations show an extremely high sensitivity to calcium, which may explain the complex results of Townes and Brown.

Because contraction can occur while metabolic activity and ATP-splitting are presumably absent, a different source of energy must be found. This may be the chemical potential of the calcium ions. It is interesting to compare the work available from this source with the mechanical work done by the spasmoneme in pulling the body of the ciliate down towards the point of attachment of the stalk. A minimum value for the work of one contraction *in vivo* can be calculated by treating the body of *Vorticella* as a sphere moved at uniform velocity against viscous drag. From Stokes's formula, the work *M* ergs, required to move it *d* cm (equal to the extended length of the stalk) at *v* cm s⁻¹, is $6\pi rnv d$, where *r* is the radius of the body in cm and *n* the viscosity of the medium in poises. For *Vorticella*^{3,4}, *r* = 0.002, *n* = 0.01, *v* = 2.3 and *d* = 0.008, hence *M* = 6.9 × 10⁻⁶ erg. Assuming that the radius of the spasmoneme is 0.5 μm, this corresponds to an instantaneous power during contraction of 2,300 calories g⁻¹ h⁻¹. Contraction can be elicited experimentally by changing the calcium level from 10⁻⁸ to 10⁻⁶ g ions/l. The maximum work, *W* ergs, available to a system which takes up one g ion at a higher level *a*₁ and releases it at a lower level, *a*₂, is given by

$$W \neq RT \log \frac{e a_1}{a_2}$$

where *R* is the gas constant in ergs degree⁻¹ mol⁻¹ and *T* the absolute temperature. Putting *a*₁ as 10⁻⁶, *a*₂ as 10⁻⁸ and *T* as 293, one obtains *W* = 1.1 × 10¹¹ ergs. If it is assumed that the cell varies the activity of calcium ions between these levels and that contraction and relaxation result from the uptake and release of calcium by the contractile material, the amount that must be taken up is *M/W* or 6.9 × 10⁻¹⁷ g ions/spasmoneme. This is a small quantity: it is equal to the amount of calcium in a 1.1 mM solution of calcium chloride of the same volume as the spasmoneme.

Hoffmann-Berling suggested that the contractile material might consist of long molecules held in extension by the mutual repulsion of negative charges distributed along their length. Calcium ions, by neutralizing the charges, could allow the molecules to fold under internal forces or thermal agitation. Certain observations with the light microscope seem to be relevant to this theory. The spasmoneme of the living stalk of *Carchesium*, which is similar to that of *Vorticella* but larger, is positively birefringent with respect to its length. The mean of ten measurements of the birefringence was 4.5 × 10⁻³ and the standard deviation 0.7 × 10⁻³. During the coiling of the stalk the spasmoneme shortens by 64 ± 8% and the birefringence falls, as observed by Schmidt⁵. By treatment with 25 mM caffeine, it has been possible to retard the extension after contraction, and thus to establish that the birefringence just after contraction is too low to be detected with a λ/30 compensator of the Brace-Köhler type. Presumably the spasmoneme becomes totally isotropic in contraction.

It has been assumed that the extension of the stalk is produced entirely by the elastic recoil of the sheath. In living stalks trapped in a thin film of water, however, the spasmoneme often seems to extend while the surrounding sheath is motionless. A cycle of changes in shape is observed. The spasmoneme

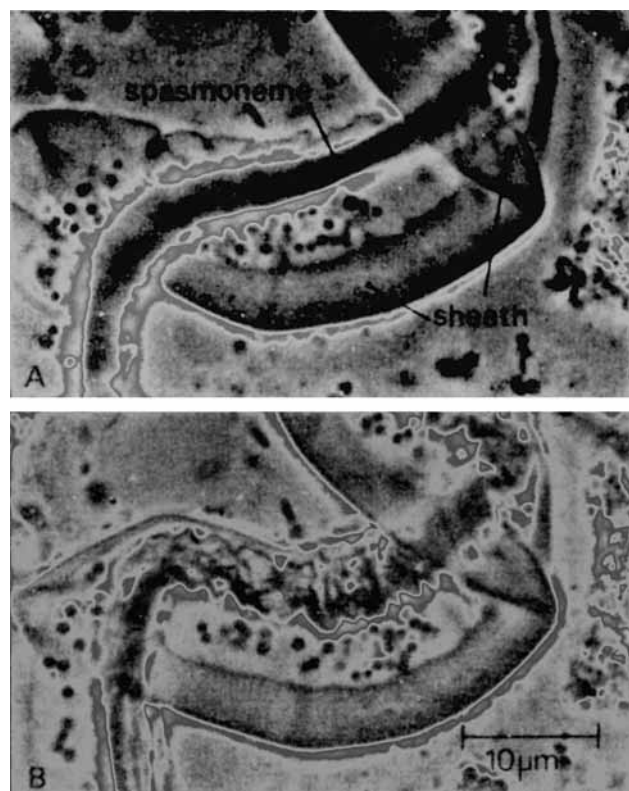


Fig. 1 Photographs taken approximately 5 s apart, showing stages in the spontaneous cyclic changes in shape of a spasmoneme of *Carchesium* sp. The stalk is intact but flattened between slide and coverslip in order to restrict its movement. (Phase contrast.)

seems to grow suddenly straight and dark in positive phase contrast (Fig. 1A). It then splits into longitudinal strands (Fig. 1B) which seem to elongate, becoming sinuous, perhaps helical. After several seconds the strands suddenly contract and fuse into a homogeneous dark body as before. The model proposed by Hoffmann-Berling might extend actively on the removal of calcium ions.

Carasso and Favard⁶ have demonstrated cytochemically the accumulation of calcium within a system of tubules running throughout the spasmoneme of *Vorticella* and *Carchesium*. Because MgATP has a relaxing effect which occurs only in the absence of the calcium buffer, it is not unlikely that in life the state of contraction of the spasmoneme is controlled by an MgATP dependent pumping of calcium into these tubules. A sudden release of calcium would make available to the contractile apparatus the chemical potential built up over a long period by the pump. Such a theory would explain the very high instantaneous power, which is about 500 times greater than the average power of human skeletal muscle.

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Environmental DDT and the Genetics of Natural Populations

DDT* residues have already been implicated in widespread disruption of various ecosystems¹⁻¹⁰. We report here the possibility of their being indirectly responsible for alterations in the genetic content of populations. Our conclusions are based on correlations between chromosomal changes in the fly *Drosophila pseudoobscura* described over the past 24 years in the western US by Dobzhansky and various collaborators and the distribution patterns of DDT residues we are finding throughout this area. In addition to general geographic correlation, there are several episodes in which these particular genetic effects occurred immediately after DDT application in the particular areas involved.

On the basis of different inversions and combinations of inversions occurring in the third chromosome of *Drosophila pseudoobscura*, several different forms of this chromosome were shown to occur in natural populations of this fly¹¹. Because these were not distributed uniformly, the different chromosomal forms were named according to the area of their discovery. Those most relevant to this study are 'Arrowhead' (abbreviated AR), 'Chiricahua' (CH), 'Pike's Peak' (PP), and the reference configuration, of which the others were considered inversions, 'standard' (ST).

Use of the "population cage"¹² and other experimental techniques¹³ showed that these different chromosomal forms had specifically differing genetic effects. They can therefore be regarded as a series of multiple alleles¹² responding differentially to different selective regimes on the basis, for example, of temperature^{13,14}, relative humidity¹³, species of food yeast¹⁵, or geotactic selection¹⁶.

Meanwhile, it was found that in a given locality, natural populations of the fly did not remain constant in percentage composition with respect to the different forms of this chromosome, but changed with time. Some of these changes followed a yearly cycle apparently in response to the changing selective pressures of the yearly seasonal cycle¹⁷⁻¹⁹. Other local changes of longer time period seemed to follow prolonged meteorological changes—for example, drought—or more often eluded explanation²⁰⁻²².

Over a period of several years it became evident that one type of change was occurring progressively in time over a great area. This change in the populations involved increase in percentage of ST and PP chromosomes, and decrease in AR and CH. This type of change was first found¹⁷ on the western face of the San Jacinto Mountains (Fig. 1), then at Mather (Fig. 1)^{18,20}, and subsequently in many places in California, Arizona, Colorado and Utah²¹. Further reports^{22,23} showed that these particular changes had continued to increase in intensity of expression. In the 1966 report geographic coverage was increased, and the same changes were shown to have occurred throughout Oregon, Washington and into British Columbia; in Nevada (Tamarack Lake; Lemoile), Arizona (Grand Canyon), Mexico (San Pedro Martir Mountains, Baja California) and through New Mexico into Texas. The changes were greatest in central to southern California, declined somewhat to the north, but were expressed strongly throughout Oregon and Washington. To the east of California, strength of expression declined gradually eastward. Explanations of the phenomenon in terms of meteorological trends¹⁷⁻²⁰ or as the effects of fires¹⁷ proved untenable^{21,24}. Human interference at first seemed out of question in the remote areas involved, though in 1964 Dobzhansky *et al.*²² speculated on the possible role of insecticides, especially DDT, transported

* Term used here to indicate both the more common *p,p'* isomer and the less common *o,p'* isomer of DDT, as well as their metabolic derivatives, especially *p,p'*-DDE. Chemically, *p,p'*-DDT is 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; *o,p'*-DDT is 1,1,1-trichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane; *p,p'*-DDE is 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene.

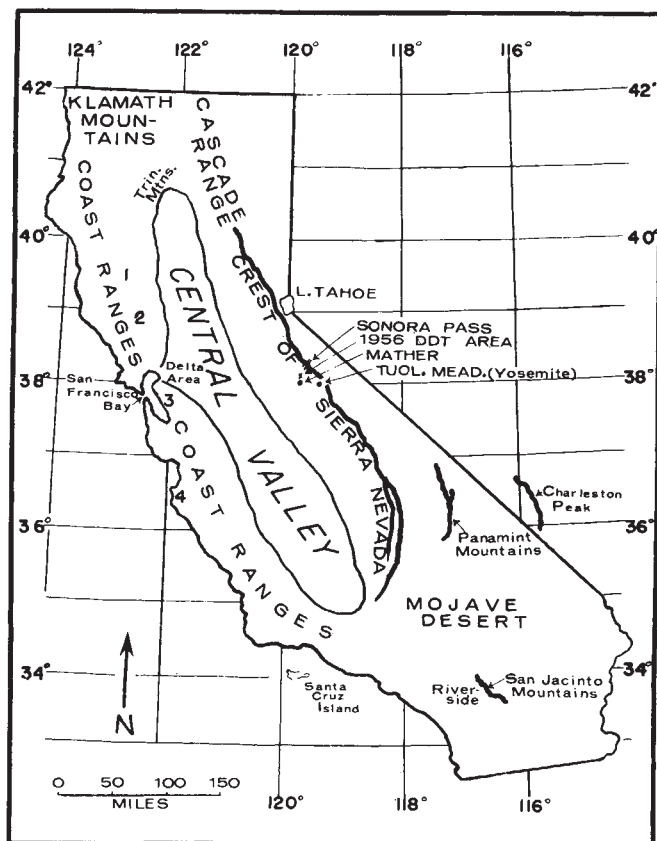


Fig. 1 Map of California, showing especially the geographic location and relationship to each other of the central valley and the Sierra Nevada Mountains. Numbered locations in the northern and southern coast ranges are the sites of collection of some of the specimens listed in Table 1.

from California by wind in a manner now known to be entirely feasible^{25,26}.

In the central valley area of California (Fig. 1), enormous amounts of pesticides are applied in crop-dusting by airplane. Records of exact amounts have not been kept, but conservative estimates (Robert Rawlins, California State Department of Agriculture, personal communication; Dr Eldridge Hunt, California Department of Fish and Game) show that thousands of tons of DDT alone have been thus used annually in California agriculture. The predominantly westerly winds across the valley would carry much DDT eastward which would then be deposited with precipitation. The Sierra Nevada Mountains, especially, would be expected to receive pesticide residues, for they extend in approximately a north-south direction parallel to the valley and immediately to its east.

Our search for residues in the mountains has been described in detail elsewhere¹⁰. We used frogs because of the concentration of their fatty tissues into a discrete pair of fat bodies, their position well along the chain of secondary consumers ecologically and previous knowledge²⁷ of their distribution throughout the mountains. Fat bodies were extracted with hexane after digestion in a mixture of perchloric and acetic acids and destruction of fats with fuming sulphuric acid. The product was identified by gas-liquid chromatography. Recent further confirmation has been provided as to the reliability of our identifications*. Our investigation was limited to *p,p'*-DDE because this was the chlorinated hydrocarbon we found most consistently and in greatest abundance.

* Provided by Mr James Ferguson, of the California State Department of Public Health, Berkeley, California. Thin-layer co-chromatography of a random pool of 50 of our samples with authentic compounds of the DDT family (*p,p'*-DDT, *p,p'*-DDE and *p,p'*-DDD) has verified our identifications of peaks on our GLC chromatograms.

Table 1 of our previous report¹⁰ summarized the distribution of DDT residues thus revealed in the Sierra Nevada. Table 1 of this article shows the distribution in areas other than this mountain range. Our first conclusion from these data is that contamination of the western US with DDT residues is general, and in quantities readily detectable in biological systems. As with the chromosomal changes summarized above, concentrations are greatest from central to southern California and decline to the east, which is consistent with wind-borne distribution from its central valley. The finding of greater concentrations in the south is consistent with the greater area and more intense agriculture of the southern part of the valley. The abrupt decrease in concentration at the Sierra Nevada crest¹⁰ supports the idea that pesticide fall-out is related to precipitation patterns, this crest being the western boundary of the desert areas of the south-western US. The unexpectedly high concentrations in the Yosemite-Sonora zone (from about 37° 40' to 38° 20' N; ref. 10) are attributed to two massive applications of DDT to forests in this region (reports by courtesy of Dr G. R. Struble of the US Forest Service). The first of these²⁹ was in 1953 in the Tuolumne Meadows area, the second³⁰ in 1956 in an area about 25 miles north-west of this (Fig. 1). This long persistence is consistent with previous work³¹ after single application to a forest. Applications of DDT to forests have been rare in California. These two and one north of the Sierra Nevada are all that we can find recorded.

Table 1 Summary of Distribution of Frog Fat Body *p,p'*-DDE in p.p.m. in Areas outside the Sierra Nevada Mountains of California

Region	No. of localities	No. of samples	Average p.p.m. DDE
California (Fig. 1)			
Trinity Alps area : 40° 57'–41° 2' N lat., 122° 53'–122° 59' W long.	4	11	0.33
Coast ranges north of San Francisco bay	2	3	0.73
Coast ranges south of San Francisco bay	2	2	3.92
Nevada			
Tamarack Lake : Washoe County, 39° 19' N lat.–119° 54' W long., 9,000 feet altitude	1	1	0.46
Lemoile : western foot Ruby Mountains, 40° 42' N lat.–115° 28' W long.	1	2	0.12
Arizona			
Grand Canyon, near junction of Kanab Cr. with Colorado River	2	19	0.70
Baja California, Mexico			
Tassajera Canyon, San Pedro Martir Mountains, 31° 2' N lat.–115° 24' W long., about 5,000 feet altitude	1	2	1.04

All samples from yellow-legged frogs (*Rana boylei*) except the Arizona and Baja California samples from tree-frogs (*Hyla* sp.) and the Lemoile (Nevada) samples, which are whole-body juvenile toads (*Bufo* sp.).

The findings of Dobzhansky *et al.*²³ that chromosomal changes were relatively uniform and strong throughout Oregon and Washington and into southern British Columbia (Fig. 2) seem at first to contraindicate DDT as a causative factor. Throughout the 1940s and 1950s, however, millions of acres of forest in Oregon and Washington were sprayed aerially with DDT³², so that whereas genetic changes in California and the south-west could be caused by drift of agricultural DDT from the valley along with two isolated forest sprayings, changes in the north-west could be explained on the basis of widespread and long-continued forest sprayings.

If some of the data from Dobzhansky's publications (Table 2) on behaviour of ST, AR, CH and PP chromosomes are studied in the light of the use of DDT in California, some remarkable correlations emerge. Because the chromosomes show seasonal variation, changes at Keen Camp on the western

face of the San Jacinto Mountains (Fig. 1) should be studied on a monthly basis. ST reached a value of 52% in April of 1946, the highest April value in the study. The June peak, 48%, also occurred in 1946. For AR, the minimum April value, 15.5%, occurred in 1946, and also the June low of 15%. For CH, an April low of 23.7% and a June low of 32.5% were both in 1946. Thus 1946 was a year of all-time highs for ST and all-time lows for AR and CH, the sort of genetic upheaval that occurred throughout the western US (the PP chromosome not having been found here yet). It is significant that DDT was licensed for use in California agriculture in September 1945, when it was immediately rushed into use, especially in early 1946 (personal communication from Robert Rawlins, California State Department of Agriculture). Keen Camp, being on the western face of the mountains (Fig. 1), is immediately adjacent to the heavily agricultural Riverside Valley, and the genetic changes at this time were evident before they occurred on the eastern, or desert, exposure of the mountains at Pinyon Flat¹⁷.

Table 2 Extracts from Tables in Publications by Dobzhansky on Changes in Population Percentages of ST, AR, CH, and PP Chromosomes

Month and year		ST	AR	CH	
(a)	April 1939	32.5	30.0	32.5	
	May 1939	32.6	28.5	36.2	
	June 1939	24.8	30.8	41.2	
	July 1939	28.6	29.3	37.3	
	Aug. 1939	29.5	30.5	37.6	
	Sept.-Oct. 1939	26.0	35.7	35.1	
	April 1940	30.6	22.8	42.7	
	May 1940	26.8	22.1	47.1	
	June 1940	31.9	20.7	43.4	
	July 1940	34.5	24.8	37.4	
	Aug. 1940	37.6	26.4	31.5	
	Sept. 1940	41.2	17.6	32.4	
	May 1941	29.0	29.4	37.9	
	June 1941	38.3	17.6	39.3	
	July 1941	35.4	27.2	33.5	
	Sept. 1941	38.2	25.0	32.4	
	April 1942	45.1	17.6	29.4	
	May 1942	45.1	14.7	33.3	
	June 1942	28.2	15.4	46.4	
	July 1942	26.0	18.0	52.0	
	April 1945	41.0	22.2	29.2	
	April 1946	52.0	15.5	23.7	
	June 1946	48.0	15.0	32.5	
	Year	ST	AR	CH	PP
(b)	1945	35.7	35.7	17.2	—
	1946	30.9	36.6	17.1	0.3
	1947	30.0	39.4	20.2	0.7
	1950	20.3	49.8	17.4	2.8
	1951	29.2	43.2	11.2	4.6
	1954	27.3	36.4	12.6	11.7
	1957	45.3	33.2	3.8	9.8
	1959	39.9	35.6	10.7	4.4
	1961	64.3	14.0	3.4	6.3
	1962	53.6	27.1	2.2	8.7

(a) Populations at Keen Camp, western face of San Jacinto Mountains. PP chromosomes not yet present here (from ref. 17). (b) Pooled yearly data on gene arrangements at Mather, 1945-1962 (from ref. 24).

The data of Mather (Fig. 1) from 1945 to 1961 (Table 2b) show that ST reached an all-time peak of 45.3% in 1957 and never thereafter descended to pre-1957 values. Further, AR reached a low of 33.2% in 1957 and never again rose to pre-1957 values. CH showed a drastic decrease in 1957 and did not even remotely approach pre-1957 values thereafter. The PP type, which has been the most sensitive of all the chromosomes involved²⁰⁻²³, increased remarkably in 1954 and only once thereafter descended to pre-1954 values. Fig. 1 shows the proximity of Mather to the special spraying areas of 1953 and 1956. It is here suggested that the ST, AR and CH changes were consequences of the 1956 episode, while the seemingly more responsive PP type reacted in 1954 to the somewhat more distant 1953 spraying.

Negative results were obtained in previous experiments³³ using population cage technique¹² to test the hypothesis of DDT causation of the genetic changes under consideration. There is, however, a flaw in these methods. Adults were removed periodically from the population cages, stressed by exposure to paper impregnated with DDT, then returned to the cages. It was the adults only therefore that were subjected to DDT selection. But as pointed out originally by Wright and Dobzhansky¹², the true competition is in the larval stages, that is, in the food cups, not in the adult stage. Experiments in which DDT is incorporated into the larval food medium are therefore being initiated.

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Effects of Imprinting on Uracil Incorporation into Brain RNA in the "Split-brain" Chick

We have shown that an imprinting procedure influences the rate of incorporation of ^3H -lysine and ^3H -uracil into acid insoluble fractions from the upper part of the chick's forebrain^{1,2}. These incorporation rates reflect, although they do not accurately measure, rates of protein and RNA synthesis respectively. The effects of the imprinting procedure on the chick's brain could be brought about in a number of ways, for example, hormonal changes, frustration or increased locomotor activity, which need bear no direct relation to the imprinting process.

Some of the non-specific side-effects of visual experience can be allowed for by training one side of a chick's brain and not the other. Because the optic chiasma is completely crossed, this can be achieved by cutting the forebrain commissures and covering up one eye during the training procedure³. If both sides of the brain are influenced by non-specific factors and only one side by exposure to an imprinting stimulus, any difference between the two sides should be a direct consequence of visual experience. Here we describe the effects of an imprinting procedure on the incorporation of tritiated uracil into the RNA of three brain regions after the forebrain commissures have been cut and one eye covered during training.

We decided to split the brain because inter-ocular transfer takes place after exposing one eye during imprinting of intact ducklings⁴. Furthermore, in preliminary experiments using the same training procedure as in previous studies^{1,2}, we found that when intact chicks were trained with one eye covered, no differences in the incorporation of uracil into RNA were found between the two sides of the brain.

Eight batches of Chunky chicks were hatched and kept in a dark incubator for 1–4 h after hatching. Each chick was anaesthetized and mounted in a stereotaxic apparatus. The brain was exposed from above and a fine knife lowered between the two hemispheres until the blade was at the correct stereotaxic setting for the supra-optic commissure. The knife was then moved approximately 3 mm in the antero-posterior plane and withdrawn. The chick was then kept in the dark until the start of the experiment 18–24 h later when a small opaque cap was glued over one eye.

Table 1 Summary of Treatments in 150 min Period between Injecting Chicks with ^3H -Uracil and Killing

Condition	Length (min)	Temperature (°C)
Expose to flashing light	15	30±1.0
Darkness	15	
Expose to flashing light	15	
Darkness	15	
Expose to flashing light	15	
Darkness	15	
Expose to flashing light	15	33±0.5
Dark incubator	20	
Test exposed eye	5	24±1.0
Move patch to other eye	2	
Dark incubator	13	33±0.5
Test unexposed eye	5	24±1.0

Immediately before each chick was exposed to an imprinting stimulus, 20 μCi $5\text{-}^3\text{H}$ -uracil (1,000 mCi/mmol) in 0.1 ml. Locke solution) was injected into the heart. The chick was then placed in an activity wheel in front of a flashing yellow light placed so that the chick could turn the wheel freely when walking in the direction of the light. The chick was given a total of 60 min exposure to the flashing light. Details of the timing of exposure and of testing are shown in Table 1.

To assess the effects of training on the behaviour of the

chick, it was given two choice tests between the flashing yellow light and a flashing red light; one test was with the exposed eye, the second with the previously unexposed eye. The chick was tested in a specially-gear wheel which travelled in the opposite direction from the one in which the chick was walking. As the bird walked towards one stimulus the wheel moved away from that stimulus and so carried the bird towards the other flashing light⁵.

A total of 36 chicks were trained and tested, but only 12 were used for biochemical analysis. In six of these the left eye was exposed to the yellow flashing light, and in the other six the right eye. The criteria for selection were that the bird should show visual orientation with each eye, and show no motor impairment. Most important of all, it had to show a preference for the familiar flashing yellow light on the exposed side and no such preference on the other side. Table 2, which gives the mean distances travelled in 5 min by the test wheel, shows a marked difference between the exposed and unexposed sides.

Table 2 Distances Travelled by Test Wheel in 5 min when Split-brain Chicks were given Choices between Familiar and Unfamiliar Stimuli with Previously Trained and Untrained Eyes

	Mean (cm)	s.e.
Trained eye	+8.64	±2.59
Untrained eye	+0.58	±1.00

The test wheel was designed so that it moved in the opposite direction from the one in which the chick was walking. A positive score means that the chicks walked towards the familiar stimulus.

Immediately after the final choice test, and 150 min after injection, each chick was decapitated and its brain dissected into three regions (mid-brain, forebrain roof and forebrain base). Each region was divided into right and left halves and all six samples from the brain were placed in individual vials and kept frozen on solid CO_2 until analysis. As in previous experiments^{1,2} the vials were coded and the biochemical analyses performed blind. The samples were treated essentially as described previously^{2,6}. Specific activities (d.p.m./mg protein in sample) of the acid-insoluble fraction varied considerably between chicks. Values for all six samples from a brain were therefore standardized as percentages of the mean specific activity for that brain. The total radioactivity (pool—or acid soluble plus acid-insoluble) was measured and standardized in the same way. The relative specific activity of the acid-insoluble fraction was $5.33 \pm 0.12\%$ of the activity of the pool.

Table 3 Means and Standard Errors for Pool Values standardized as Percentages of the Mean for all Six Samples from each Chick

	Roof	Base	Midbrain
Trained	94.4±1.3	102.5±1.4	102.6±1.4
Untrained	92.2±1.3	101.1±1.3	107.3±2.2

The differences between the trained and untrained sides are not statistically significant.

The standardized values for radioactivity in the pools are shown in Table 3. In no brain region do these differ between the exposed and unexposed sides.

The mean values for the standardized specific activities are shown for the exposed and unexposed sides of each brain region in Fig. 1. The difference between the exposed and unexposed side of the forebrain roof alone is statistically significant (Wilcoxon $T=7$, $P=0.01$). This effect in the split-brain chick occurs in the same region in which we have previously detected differences between experimental and control chicks in the incorporation of lysine into protein¹ and where we have found the most rapid incorporation of uracil into

RNA as the result of exposure to an imprinting stimulus².

We conclude that the effects of our imprinting procedures on incorporation of uracil into RNA cannot be attributed to non-specific factors that affect both sides of the brain. Although it still remains possible that the biochemical differences are due to sensory stimulation as such and are not direct products of learning, these observations are to our knowledge the first evidence of differential biochemical effects between the two halves of a split-brain preparation after a learning procedure.

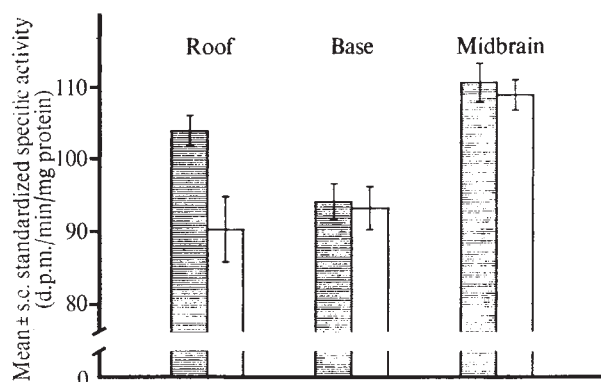


Fig. 1 Means and standard errors of standardized specific activities of RNA from trained (hatched columns) and untrained (white columns) sides of forebrain roofs, forebrain bases and midbrains of split-brain chicks. The trained side is contralateral to the exposed eye. In each case the sample size is 12.

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supplemented with human or foetal calf serum. Preliminary details of this work have been presented elsewhere⁴.

Six embryos were cultured. The pH of the medium was 7.3, the osmotic pressure 300 mOsmol/kg, and the gas phase consisted of 5% oxygen, 5% carbon dioxide and 90% nitrogen. Two of the embryos developed to early morulae, one having more than twenty-three nuclei, and the other twenty-nine nuclei and one mitosis. After the sixteen cell stage, the blastomeres of these embryos became slightly mottled and the cell outlines were less distinct—an appearance similar to that found in many mouse morulae.

A blastocoelic cavity appeared in four embryos. In two of them, the cavity was small and eccentric and the inner cell mass and trophoblast failed to become fully differentiated. Staining revealed only sixteen and twenty nuclei in the two embryos. The small number of cells indicated that division had become out of step with the early development of the blastocoel. Two embryos which developed through typical morulae into fully expanded blastocysts will be described separately.

After 123 h culture in Ham's F 10 with 20% foetal calf serum, irregular light patches appeared throughout the tissue of one morula (blastocyst 1). Eleven hours later, a large blastocoelic cavity was seen, with thin cellular membranes traversing part of it. The cavity became increasingly clear as differentiation continued. After 147 h in culture, the blastocyst was greatly expanded, and apart from one small vesicle the blastocoelic cavity was completely clear. The zona pellucida was thin and stretched, and the trophoblast formed a clear layer of cells immediately beneath the zona. The blastocoel occupied three-quarters or more of the embryo, and the inner cell mass was distinct—far more so than is usual in mouse blastocysts. Giant cell transformation was not seen, but the embryo was not examined sufficiently closely to ensure that it had not occurred. The blastocyst was cultured for a further 2 h in its original medium plus 5 µg/ml. of 'Colcemid'. During this period the blastocyst contracted away from the zona, making it unsuitable for photography.

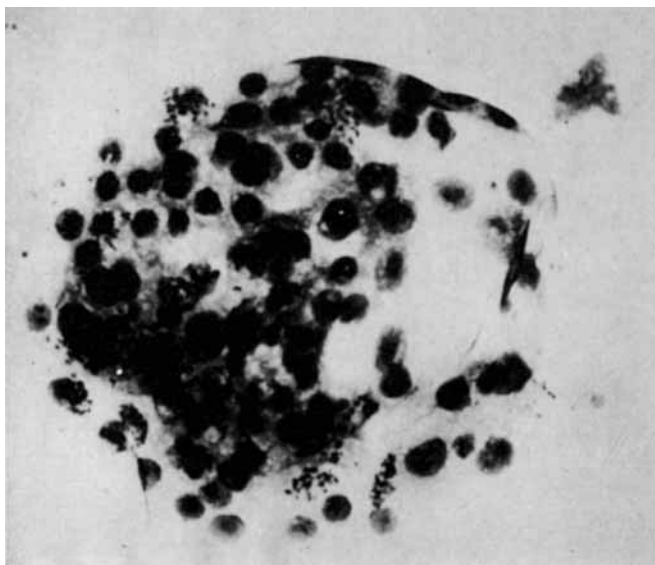


Fig. 1 Stained preparation of blastocyst 1. Many mitoses can be seen over the region of the inner cell mass (lower right) and a few elsewhere. The nuclei are even-sized.

The blastocyst was placed in 1% sodium citrate for 2 min and fixed in fresh acetic methanol⁵. After staining with aceto-orcein, it was found to possess 112 nuclei and at least sixteen mitoses (Fig. 1). Several of the mitoses overlapped in the region of the inner cell mass and were unscorable. Others were discrete but insufficiently spread so that we could only estimate that they were probably diploid.

Human Blastocysts grown in Culture

We have already described the culture of cleaving human embryos to the sixteen celled stage¹, and we now wish to give details of a few embryos that have developed much further, including two that reached fully developed blastocysts. Methods were similar to those described before. Preovulatory oocytes recovered by laparoscopy² were fertilized in Bavister's medium³, and transferred after 12–15 h into Ham's F 10

The second blastocyst (blastocyst 2) developed approximately 24 h after the other. It was cultured in Ham's F 10 containing 25% human and 25% foetal calf serum. A blastocoelic cavity appeared after 159 h in culture. This cavity corresponded with that seen in the early stages of expansion in blastocyst 1, but the cell membranes traversing it were more pronounced and persisted for 12 h. Some of the trophoblastic cells had evidently failed to release their contents into the blastocoel. The thin zona pellucida and the shape of the inner cell mass were similar to those seen in blastocyst 1. Small extensions, somewhat resembling those seen in guinea-pig blastocysts⁶, seemed to be passing through the zona pellucida (Fig. 2).



Fig. 2 Blastocyst 2 before it was fixed and stained. The thin zona pellucida and the underlying trophoblast can be seen; an extension is evidently emerging through the zona (at right). The inner cell mass (lower part of the embryo) is distinct. The cellular membranes persisting across the blastocoel can be seen.

The embryo was kept at room temperature for several hours before staining. It was found to have 110 nuclei. Bodies resembling sex chromatin were seen in a few nuclei.

We seem to have achieved this improved embryonic development through better handling of the cultures than previously. The preovulatory oocytes were kept at room temperature under reduced oxygen tension and 5% carbon dioxide until the spermatozoa were added. Small microdrops were used for culture, and enlarged when the embryos were eight celled. The embryos were left undisturbed for long periods after this stage.

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Excretion of *p*-Methoxyamphetamine administered to Humans

PSYCHOSIS can be induced by the administration of large doses of amphetamine¹ and some of its derivatives². In man, a principal metabolite of amphetamine is *p*-hydroxyamphetamine. Biological O-methylation of this compound would yield a potent hallucinogen, *p*-methoxyamphetamine (PMA)³. In a previous report⁴, we demonstrated that within the limit of detectability of PMA (about 80 µg/24 h urine) by a sensitive procedure employing gas chromatography of the acetyl derivative, PMA was not detected in the urine of four subjects to whom amphetamine sulphate was administered in large doses (mean of 629 mg) over an average period of 51 h. These subjects developed varying degrees of psychotic symptomatology.

Here we wish to demonstrate that PMA, when administered can be detected in human urine. Five normal subjects ingested 10–65 mg of PMA hydrochloride. Urine was collected in 12 h periods except when otherwise noted in Table 1. Aliquots (5 ml.) of the urine specimens were analysed in duplicate by gas chromatography as described previously^{4,5}. In this procedure, which uses phenethylamine as an internal standard, the recovery of 10 µg of PMA-HCl added to 5 ml. urine samples was 108 ± 21 (s.d.).

Table 1 Excretion of PMA in Urine

Subject and trial	Weight (kg)	Dose PMA (mg)	Time of urine collection (h)	Volume (ml.)	Mg PMA excreted	PMA excreted (%)
1 A	65	10	0–12	660	580	2.64
			12–24	320	510	0.51
			0–12	380	400	0.17
			12–24	510	230	0.08
			24–36	150	280	0.01
2	64	10	0–12	840	670	6.75
			12–24	1,020	1,280	6.15
			24–36	960	1,020	1.92
3	57	57	0–15	1,000	1,450	11.8
4	67	20	0–24	900	1,100	4.25
5	76	30	0–12	1,770	800	3.5
			12–24	1,280	1,190	1.4

The average excretion of PMA was 6.7% of the administered dose with a range of 0.3 to 15%. Variations in PMA excretion may, in part, be related to urinary pH⁶.

Because PMA was detected in the urine of subjects who received as little as 10 mg PMA-HCl (a sub-hallucinogenic dose), yet was not detected in the urine of subjects receiving about 600 mg of amphetamine, it is unlikely that PMA is formed in amounts required for psychogenesis when directly administered. The possibility of small amounts of the compound being formed at specifically sensitive central nervous system sites, of course, still exists.

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Methadone increases Mouse Brain 5-Hydroxyindoleacetic Acid

METHADONE, a synthetic narcotic with many similarities to morphine, is currently being used extensively as a crucial part of treatment-rehabilitation programmes for heroin addiction. In the doses used for "methadone maintenance", this compound has minor tranquillizing effects, blocks the euphoric effects of heroin, eliminates drug craving, and prevents narcotic withdrawal symptoms. Although the mechanism of action of methadone is unknown, there are a number of recent reports which suggest that 5-hydroxytryptamine (serotonin) is involved in the perception of pain and in the mechanism of action of narcotic analgesics. For instance, Tenen first showed that *p*-chlorophenylalanine, which depletes tissues of serotonin by inhibiting synthesis, lowered the pain threshold of rats as measured by a flinch-jump technique¹. He further found that *p*-chlorophenylalanine pretreatment lowered the analgesic effect of several major narcotics, including morphine and methadone². Lints and Harvey made lesions in the medial forebrain bundle, septal area, and dorsomedial tegmentum of rats and concluded that the resulting increased sensitivity to electric shock and decreased telencephalic serotonin content were causally related³. Both effects were reversed by L-5-hydroxytryptophan but not by L-dihydroxyphenylalanine⁴. Rogers and Thornton showed that increased serotonin levels (but not dopamine or norepinephrine levels) were highly correlated with increased toxicity of principal narcotic analgesics following monoamine oxidase inhibitors⁵. Way *et al.* found that chronic morphinization of mice followed by pargyline administration resulted in a more rapid rise in brain serotonin compared with controls⁶. These investigators also showed that tolerance of and physical dependence on morphine in these animals was antagonized by *p*-chlorophenylalanine pretreatment and related the effects of morphine on serotonin metabolism to the development of tolerance and physical dependence.

Table 1 5-Hydroxyindoleacetic Acid Content of Mouse Brain after Administration of Methadone or Morphine

Drug regimen	Brain 5HIAA as percentage change from control*
(1) Morphine 10 mg/kg 3 times daily for 1 week, then 20 mg/kg 3 times daily for 2 weeks	+111 (4)
(2) Methadone 10 mg/kg 3 times daily for 3 weeks	+163 (5)
(3) Methadone 5 mg/kg	+45 (15)
10 mg/kg	+64 (4)
15 mg/kg	+76 (8)
(4) Controls+pargyline (75 mg/kg)	-54 (4)
(5) Methadone (10 mg/kg)+pargyline	-58 (4)†
(6) Methadone (10 mg/kg)+probenecid (200 mg/kg)	+171 (4)

* Absolute control values for thirteen determinations were 211 ± 14 ng 5HIAA (free acid) per gram (wet weight) of brain. The number of determinations is in parentheses. Two brains were used for each determination.

† Controls were values for brain 5HIAA 2 h after methadone (10 mg/kg) only.

Haubrich and Blake found increased 5-hydroxyindoleacetic acid (5HIAA) in rat brain after acute and chronic doses of morphine⁷. These studies strongly support the idea that sensations of pain and certain effects of narcotic analgesics are mediated by serotonergic systems. To compare methadone to morphine with regard to serotonin metabolism we performed the following experiments.

White mice (50–75 mg) were injected intraperitoneally with saline, d-l methadone (5–15 mg/kg), or morphine sulphate (10–20 mg/kg) at varying intervals. Acute animals were killed 2 h after a single dose; chronic animals were injected three times a day for 3 weeks. In some experiments pargyline (75 mg/kg intraperitoneally) was administered with methadone and these animals were killed 2 h later. In other experiments probenecid (200 mg/kg intraperitoneally) was given 15 min after methadone and these animals were also killed at 2 h. Two mouse brains (without cerebellum) were pooled for each determination of brain 5HIAA⁸. Methadone added to brain homogenates did not produce increases in the 5HIAA measurements. Prepared parenteral solutions of morphine, methadone, and probenecid (sodium probenecid) were used. Pargyline was dissolved in physiological saline before injection.

Values for mouse brain 5HIAA in the various experimental conditions are listed in Table 1. Morphine, when administered repeatedly according to a schedule designed to produce tolerance and dependence, increased brain 5HIAA. Methadone given by a similar schedule also produced a large increase in brain 5HIAA. Acute doses of methadone (5–15 mg/kg) also produced dose-related increases in brain 5HIAA. These increases were not as great as those produced by chronic administration of methadone. Thus the increase in brain 5HIAA produced by methadone is apparent after a single dose but becomes greater after repeated doses. The results of the experiments using pargyline indicate that the slope of the decay in 5HIAA after pargyline was the same both for untreated animals and for animals given a single dose (10 mg/kg) of methadone⁹. Similarly, probenecid, used in conjunction with a single acute dose of methadone (10 mg/kg), produced an increase in brain 5HIAA which was more than twice that produced by this dose of methadone alone. The pargyline and probenecid experiments show that methadone does not increase brain 5HIAA by affecting the transport system which removes acidic metabolites from brain¹⁰. So methadone, like morphine, apparently produces an increase in brain serotonin synthesis in the mouse. It is still unclear whether such an increase results from a primary effect on the synthesis of serotonin or from an increased requirement for this amine leading to an increase in synthesis. Further, it is important to bear in mind that the catecholamines have also been implicated in the action of the narcotic analgesics^{11,12}. In this regard, important species

differences have been described in animal studies of the effects of narcotic compounds on amine metabolism¹³.

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Regular Induction of Hypomania by L-Dopa in "Bipolar" Manic-depressive Patients

ALTHOUGH the catecholamine precursor L-dopa (L-3-4-dihydroxyphenylalanine), like most clinically effective antidepressant drugs, reverses reserpine-induced brain catecholamine depletion and sedation¹⁻³, early clinical trials using 1.5-3.0 g/day revealed no significant antidepressant activity⁴⁻⁹. Recently, we gave L-dopa to eighteen depressed patients, using the very large oral doses found to be effective in reversing many of the symptoms of Parkinson's disease¹⁰⁻¹⁷.

For most patients, generally negative antidepressant results were again observed (refs. 18-21 and our unpublished observations). Six of the seven manic-depressive patients in this group, however, became hypomanic while receiving L-dopa. The development of hypomania seems particularly interesting in the light of evidence implicating an excess of brain catecholamines in mania (refs. 23-26 and unpublished results of W. E. B., G. F. Borge, F. K. G., and D. L. M.).

L-Dopa was administered in double blind conditions with placebo periods before and after active drug periods and with frequent rotation of drug code sequences. Independent diagnostic assessment before drug administration and twice-daily behavioural ratings using a fifteen-point, twenty-five-item scale were made as described before^{9,26}. The presence or absence of a well documented history of mania was used to differentiate the seven manic-depressive ("bipolar") patients from eleven other psychotically depressed ("unipolar") patients. This classification is consistent with the reports of Perris²⁷ and others^{28,29} which suggest that bipolar and unipolar depressed patients can be separated on genetic, clinical and biological grounds.

The eighteen patients hospitalized for depression were treated with L-dopa in gradually increasing doses beginning with 1-2 g/day. Eleven patients (five bipolar and six unipolar) received the drug alone in maximum doses of 4.0-12.5 g/day, while the other seven received L-dopa in smaller amounts (0.3-1.6 g/day) together with *d,l*- α -methyl dopa hydrazine (MK-485) (0.75-1.50 g/day). The latter drug inhibits aromatic amino-acid decarboxylase in the periphery but not in brain, thus lowering the dose of L-dopa needed to achieve effective brain concentrations and avoiding some peripheral side effects^{21,30}.

Seven of the eighteen patients treated with L-dopa manifested brief but typical hypomanic (six patients) or manic (one patient) episodes characterized by increased motor and verbal activity with pressured speech, increased social involvement, intrusiveness, increased expressed anger, provocativeness, marked sleeplessness and some euphoria and delusions of grandeur. These hypomanic episodes were indistinguishable from spontaneous hypomanic episodes by the patient's retrospective judgment or by the blind observers' ratings and descriptions, except for one patient who manifested marked anxiety and physical discomfort (related to gastrointestinal symptoms) together with typical hypomanic hyperactivity, pressured speech and singing. One male patient invited groups of female patients and staff to come to bed with him; no other apparent increase in sexual arousal accompanied hypomania in these patients. Mean ratings for the seven patients on the global mania scale increased from 1.0 ± 0.1 in the 5 days preceding the hypomania to 4.7 ± 0.3 during the 2-4 day hypomanic periods ($P < 0.001$).

The incidence of hypomania in the bipolar patient group (85%) was markedly higher than that in the unipolar depressed patients (9%; $\chi^2 = 7.6$, $P < 0.01$). Maximum L-dopa dosage and duration of treatment with L-dopa were very similar in both patient groups (Table 1). In eight recent reports of L-dopa administration in similar dosage to 394 patients with Parkinson's disease, hypomania was described as a side effect in only three patients (<1%), whereas the average incidence of other psychiatric side effects conceivably representing hypomanic-like symptoms (such as agitation and confusion) was 10-15%¹⁰⁻¹⁷.

Table 1 Characteristics of Patients and Doses of L-Dopa in Relation to the Occurrence of Hypomania in Eighteen Depressed Patients

	Hypomania (N=7)	No hypomania (N=11)
Manic-depressive (bipolar) patients	6	1
Psychotic depressive (unipolar) patients	1	10
L-Dopa maximum dose (mg/kg)	$95 \pm 15^*$ (14 ± 0)	95 ± 16 (12 ± 2)
L-Dopa treatment duration (days)	27 ± 7	30 ± 6
Age (years)	45 ± 3	50 ± 5
Sex	4 M, 3 F	5 M, 6 F

* Mean $\pm$ s.e. The seven patients given the decarboxylase inhibitor, MK-485, received the dose of L-dopa shown in parentheses.

The one patient in the unipolar group who developed hypomania during L-dopa treatment had been described previously as being cyclothymic, with some periods of mild euphoria associated with over-talkativeness, but she had never had a definite manic episode nor received treatment for these symptoms. She was the only patient in the group developing hypomania whose depression clearly improved during L-dopa administration^{18,19}. In other patients, depression ratings changed minimally or only transiently during the brief hypomanic episodes ($P > 0.4$). This lack of change in depressed mood in spite of L-dopa doses large enough to induce hypomania suggests that depression and hypomania are separable processes and do not represent the hypothesized opposite poles of catecholamine deficit (depression) and excess (mania)²²⁻²⁴.

The hypomanic episodes seemed to be directly related to the administration of L-dopa: in four of the seven episodes a reduction in dose or discontinuation of L-dopa was followed by disappearance of the hypomanic symptoms within 24-48 h. In one case an increase resulted in a recurrence of hypomanic behaviour. Moreover, none of the hypomanic episodes occurred during the period of L-dopa administration at a dosage below the amount thought necessary to affect brain amines (3.0 g/day)¹⁰⁻²⁰. The average duration of treatment with this dose (6.9 days) was only slightly less than the period

when the dose was more than 3.0 g/day before the onset of hypomania (7.8 days). The greater incidence of hypomania when the dose of L-dopa was greater (adjusted for the exact number of days in each period) is statistically significant ($\chi^2 = 5.7$, $P < 0.05$).

These results suggest that the catecholamine precursor, L-dopa, induced typical hypomanic behaviour in patients with previous episodes of spontaneous mania. Increased motor activity and aggressiveness in rodents and in primates correlate directly with increased concentrations of catecholamines in the brain after administration of L-dopa³, but whether dopamine, noradrenaline, a catecholamine metabolite or a competitive effect on the metabolism of serotonin or other amines is responsible for the behavioural effects of L-dopa remains controversial³¹⁻³⁶.

In man, several reports have suggested that mania is triggered by some drugs known from animal studies to increase functional brain catecholamines^{22,24} and suppressed by the catecholamine synthesis inhibitor, α -methyl-p-tyrosine (our unpublished results). A regular increase in urinary catecholamine excretion and a decrease in rapid eye movement (REM) sleep occur in the 24 h preceding the onset of full manic behaviour²⁵. Similar increases in urinary dopamine and homovanillic acid (HVA) excretion, increases in cerebrospinal fluid HVA, and decreased REM sleep, together with augmentation effects on visual cortical evoked responses, were observed in these patients, and suggest that both central and peripheral catecholamines were altered by L-dopa^{20,21}.

The hypomanic response reported here may prove to represent a combination of an excitant or stimulant effect of L-dopa plus a prerequisite susceptibility for mania which is found in bipolar manic-depressives. Whether this susceptibility represents a specific sensitivity to an L-dopa load in amine metabolic pathways, or a less specific psychological or other biological sensitivity to the psychomotor activating effects of L-dopa, remains to be determined.

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Medical and Ecological Considerations of L-Dopa and 5-HTP in Seeds

It is well known that 5-hydroxy-L-tryptophan (5-HTP) occurs in low concentration in mammalian brain serving as the precursor of 5-hydroxytryptamine (5-HT, serotonin). Furthermore, 5-HTP but not 5-HT can pass readily across the blood-brain barrier so that the physiological effects associated with an increase of 5-HT in the brain may be induced in rats and dogs by the interperitoneal injection of 5-HTP^{1,2}. A recent report indicated that 5-HTP produced improvement in a patient suffering from the Parkinson-like symptoms of chronic manganese poisoning after treatment with L-3,4-dihydroxyphenylalanine (L-dopa) had aggravated his condition³.

In mammalian tissues the rate-limiting step in the biosynthesis of 5-HT is the hydroxylation of L-tryptophan and 5-HTP does not accumulate where the enzyme balance favours its decarboxylation rather than its biosynthesis. This particular balance of hydroxylase and decarboxylase activity is not common to all living systems, however, and 5-HTP accumulates in high concentration (6-10% fresh weight) in the mature seeds of *Griffonia simplicifolia*, a West African legume of reputed physiological activity⁴⁻⁶.

Quickening interest in the use of L-dopa in the treatment of Parkinsonism⁷ leads us to point out that comparable differences in the relative activities of the enzymes responsible for the synthesis and decarboxylation of this amino-acid also exist between animals and plants. Like 5-HTP, L-dopa is rapidly decarboxylated in mammalian tissues and indeed the liberation of 3,4-dihydroxyphenylethylamine (dopamine) from this compound after it has entered the brain probably accounts for its beneficial effects in Parkinsonism⁷. The same ratio of hydroxylase:decarboxylase activity is not necessarily found in plants, however, and the accumulation of free L-dopa in certain species has long been known⁸⁻¹⁰. The richest source of this amino-acid so far reported is the seed of *Mucuna pruriens* from which Damodaran and Ramaswamy¹⁰ isolated L-dopa in amounts equivalent to 1.5% of the seed weight. We now report that the seeds (excluding the seed coats) of six species of *Mucuna* (including those of *M. pruriens*) which we have analysed contain between 5.9 and 9.0% of free L-dopa.

Table 1 L-Dopa Content of *Mucuna* Seeds

	Species	Weight of whole seed (g)	L-Dopa in seed (excluding seed coat) (%)
1	<i>M. andreana</i> *	6.0	6.3
		7.6	8.9
		9.4	6.9
2	<i>M. pruriens</i> †	0.4	6.4
		0.4	5.9
3	<i>M. mutisiana</i> ‡	7.4	6.8
		7.3	6.3
4	<i>M. holtoni</i> §	6.8	6.4
		6.2	7.5
5	<i>M. urens</i> §	6.3	6.4
		4.8	7.4
6	<i>M. sloanei</i>	2.8	8.7
		3.5	9.0

* Collected 15 miles north of Puntarenas on Pan American Highway, Puntarenas Province, Costa Rica, February 13, 1970. The range of values obtained for 20 seeds of *M. andreana* showed that whilst the two smallest seeds contained the smallest percentages of L-dopa, the seeds with the largest amounts of the amino-acid were medium sized. The largest seed measured contained less L-dopa than the medium sized seeds.

† Collected on the Isla Providencia, Colombia, August 24, 1969.

‡ Collected on the Isla Providencia, Colombia, August 25, 1969.

§ Gift of Dr W. H. Tallent, USDA Northern Utilisation Research and Development Division, Peoria, Illinois.

|| Gift of Mrs J. Morton, Morton Collectanea, University of Miami, Florida.

The seed embryos from which the seed coats had been removed were finely ground and 100 mg of each extracted three times with 2 ml. ethanol/0.02 M HCl (1:1) containing 1% ascorbic acid. After centrifugation, an aliquot of the combined extracts was diluted with buffer solution (0.38 M sodium citrate adjusted to pH 2.2) and the L-dopa content determined by comparison with standard solutions using a Beckman 120 C amino-acid analyser (10 cm column of Beckman resin PA 35 at 32.5° C; buffer solution (pH 4.25) (0.38 M Na⁺) flowing at 50 ml./h). The hard pigmented seed coats, which did not contain L-dopa, accounted for 15–20% of the whole seed weight in representative samples of *M. andreana*, *M. holtoni* and *M. pruriens*, 20–30% in samples of *M. mutisiana* and *M. urens* and 30–40% in samples of *M. sloanei*.

Analytical values showing the content of three seeds of *M. andreana* and of each of the other five species are given in Table 1. Confirmation of the identity and configuration of the amino-acid has been obtained by isolating it from seeds of *M. mutisiana* using a method which will be described elsewhere.

Although our immediate purpose here is to draw attention to a rich source of L-dopa which may be of use in medicine, the high and surprisingly uniform concentration of the amino-acid in the seeds of all five species of *Mucuna* raises the interesting problem of its significance in the seed. When the distribution of an unusual amino-acid is limited to a number of species that are closely related in other respects, then it is probable that these species are all derived from a common ancestral form in which the genome controlling the synthesis of the unusual amino-acid first arose; the presence of the unusual amino-acid thus serves as a good phylogenetic marker. The original mutant strain of *Mucuna*, whose seeds contained a high concentration of L-dopa, would only have replaced existing strains, however, if this trait conferred some net advantage on the individuals displaying it. A concentration of 6–9% L-dopa in the seed embryo represents a principal commitment both of those metabolic resources available to the parent plant for reproduction, and of the seed's storage potential. Yet it is a commitment made by all species analysed. The presence of a large concentration of any compound in a seed suggests storage, and it is likely that the seedlings of these *Mucuna* species metabolize L-dopa during their development. If, however, storage is the only function of this amino-acid, it is difficult to understand why selection has not favoured a genotype in which one of the precursor "protein" amino-acids such as phenylalanine or tyrosine is stored, for L-dopa requires additional enzymes for its synthesis and degradation.

The freedom from insect and small mammal attack exhibited by large legume seeds generally¹¹, and *Mucuna* seeds specifically¹², suggests an additional protective role for the L-dopa. Of the many hundreds of bruchid beetles that attack legume seeds, only the larvae of *Caryedes brasiliensis* and a closely related species can feed successfully on *Mucuna* seeds, and during the initial stages of this coevolution, there must have been a strong selection favouring the evolution of a bruchid genotype capable of metabolizing or detoxicating L-dopa. All three of the medium-sized seed-eating mammals (*Sciurus*, *Dasyprocta*, *Cuniculus*) that live in areas of Central America where *Mucuna* species grow reject the opened seeds after eating a small amount (0.5 to 1 g) when first offered them. These same animals feed readily on immature seeds of *Mucuna* and on other large legume seeds that are protected from insects by other than chemical means¹².

The narrow range of L-dopa concentrations found in all the seeds is consistent with a protective role; the seeds of genotypes producing lower concentrations would be susceptible to attack by a wider range of insects and animals (even now, large animals can eat the seeds as a purgative or diuretic¹³). Seedlings from seeds with excess concentrations of L-dopa would, on the other hand, be at a disadvantage when in competition with seedlings using a higher proportion of their seed reserves for normal vegetative purposes. No alkaloids were detected when chromatograms of seed extracts were developed with Dragendorff's reagent, and although several unidentified compounds were detected when the chromatograms were developed with ninhydrin, the areas and intensities of the unknown "spots" were very much less than those of L-dopa.

These findings strengthen our belief that the relative immunity of these seeds to insect attack may be due, in part at least, to the high concentrations of L-dopa which they contain. We also feel that this type of ecological relationship may have many parallels. The accumulation of canavanine (an arginine antagonist in many organisms¹⁴) in seeds of *Canavalia* and *Dioclea* may well be another example of such a system and it is of interest that the host-specific bruchids that feed on these seeds are also in the genus *Caryedes* (J. M. Kingsolver, personal communication). Direct evidence for this hypothesis is being sought by means of feeding experiments with a variety of insect larvae.

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BOOK REVIEWS

Origins of Mythology

Hamlet's Mill: An Essay on Myth and the Frame of Time. By Giorgio de Santillana and Hertha von Dechend. Pp. xiv + 505. (Macmillan: London, November 1970.) 84s.

Professor Giorgio de Santillana and Professor Hertha von Dechend have produced a work of great learning for which no scholar of equal stature will have anything but respect. In its own field it fully achieves its aims. For the benefit of non-specialists, however, some words of explanation are necessary.

First, the title. This will cause mystification to all but the most erudite. In Scandinavian mythology, the Icelandic original of Hamlet was a hero named Amlodhi. He was identified, "in the crude and vivid imagery of the Norse", by the ownership of a fabled mill. This mill in Amlodhi's own time ground out peace and plenty, but in later, more decadent, times it ground out salt, and finally, having landed at the bottom of the sea, rock and sand. This was the well-known Maelstrom, "the grinding stream", which was supposed to be a way to the land of the dead.

In this book the authors set out on a long intellectual journey to discover the mill's significance. They voyage through many lands and civilizations as far apart geographically and culturally as ancient Greece and the Mexico of the Mayas. Persia and India are thrown in for good measure, and in Europe the voyage takes them from the Arctic Circle in Finland to most of the Mediterranean shores.

On the way they make an almost bewildering series of references to beliefs, legends, superstitions and significant statements discovered in other books. Most of these are documented in a bibliography thirty pages long which itself must have taken weeks to prepare and check.

In addition there are numerous line reproductions of subjects as varied as Mesopotamian cylinder seals, calabashes from the Guinea coast of Africa, signs of the Zodiac from Roman Egypt, the Maya Codex, and Athanasius Kircher's concept of the subterranean flow of rivers. There are very few reproductions of photographs, which is fortunate because these are unworthy of the physical production of the work as a whole. The scholarly trappings include a self-effacing preface by Professor de Santillana, an introduction, a list of abbreviations and no less than thirty-nine appendices occupying 98 printed pages. The index is useful and the entries well chosen.

Now what does all this effort add up to? What do the authors conclude? They conclude, to put it at its briefest, first, that all the world's great myths have a common origin, and second, that the places referred to in the myths are not on the earth but in the heavens. In short, myth was the way in which astronomical observation was interpreted and the knowledge it led to passed on.

My criticism of the work does not concern the quality of the scholarship displayed which is, as might be expected, impeccable. It is based on a feeling that scholarship can be overdone and can dry up the spirit of life in a subject. To devote such immense labour to presenting a theme of this kind at a length of 505 pages, including all the appendices, is rather like using a sledge hammer to crack a nut. One thinks of the people, the lands and the cultures referred to; the immense vitality of the questing human beings of the past, as frightened, as courageous and as full of joy and tears as we are today. One thinks of—and longs for—"the crude and vivid imagery of the Norse".

In ancient Greek times subjects of profound significance to man were discussed by Socrates and his fellows with lively informality, and Herodotus told the stories of his travels in gay and gusty prose. The richness of life is as apparent today in these writings as it was more than two millennia ago. The present book, sadly to my mind, belongs more to the world of the Middle Ages, when the value of a scholar's work was largely assessed by his knowledge of the writings of other scholars. For me, *Hamlet's Mill* evokes the atmosphere of a cultured common room rather than the spirit of deeply felt personal experience.

RICHARD CARRINGTON

Government Below Ground

Beneath the City Streets: A Private Enquiry into the Nuclear Preoccupations of Government. By Peter Laurie. Pp. viii + 247. (Allen Lane, The Penguin Press: London, October 1970.) 42s.

MR LAURIE, a free lance journalist, has done some diligent digging and pieced together a quite detailed picture of the British government's preparations for dealing with a nuclear attack and its aftermath. He provides us with maps of everything from emergency electrical grids to food storage depots and networks of secret tunnels under London. Where official data are unavailable, he fills in

with guesses which seem at least plausible. He speculates on unpublicized civil defence functions of a number of "government citadels", and even suggests possible locations for the emergency seat of national government.

For his detective work, the author rates high marks; unfortunately, he also has some very foolish things to say about nuclear war, its effects on people, and the prospects for recovery in case it should occur. Mr Laurie belongs to the "nuclear war is not all that bad" school. He is convinced that the destructiveness of nuclear weapons has been much exaggerated: the perennial British overcast will blunt the effects of thermal radiation; the brick buildings will cut down on blast damage; and so on. Mr Laurie shrugs off millions of casualties in the best Herman Kahn manner. For example, he blithely dismisses the damage which a one-megaton explosion can inflict on a city like London as "negligible", pointing out that it would kill only about as many people (310,000 is his estimate) as ordinarily die from natural causes in two years! He takes comfort in the fact that it would be "very difficult" for an attacker to kill more than 37 per cent of the British population. If those assessments strike the reader as somewhat callous, there is worse to come. At the end of a chapter entitled "Recovery From a Nuclear War", Mr Laurie presents us with an extraordinary catalogue of benefits which Britain stands to derive from a large scale nuclear attack. Such an attack would at least (and I quote verbatim):

"(i) Demolish most of Britain's slum houses.

(ii) Reduce the population to thirty-five million, a level which some people feel would be quite comfortable for these islands.

(iii) By the end of the recovery period the ratio of population to fixed assets might be higher* than it had been before the attack—the survivors would be better off.

(iv) It would decentralize government.

(v) And solve the balance of payments problem".

One is tempted to compare this remarkable passage with Dean Swift's *Modest Proposal*. But alas, Mr Laurie is completely serious.

Estimating the rate of recovery from a large scale nuclear war is at best a highly uncertain exercise. Past experience is an unreliable guide, because so many of the problems to be faced would be totally

* From the context, it seems the author meant to say lower.

without precedent. There are no data, for example, on how a society is likely to react after a third of its entire population is killed in a single day. The conclusions of even a thorough study of the recovery problem would therefore have to be regarded with a high degree of scepticism. Yet Mr Laurie, after a very superficial analysis based on capital investment rates, assures us that "in something like twelve years we should be back to normal". In my judgment, this is not only nonsense but dangerous nonsense. Fostering such complacency can only make the public more receptive to the idea that initiation of nuclear war by the West is a rational possibility to be entertained under some circumstances. That would indeed be a tragedy.

LEO SARTORI

The Commonwealth List

Commonwealth Universities Yearbook, 1970: A Directory to the Universities of the Commonwealth and the Handbook of their Association. Edited by J. F. Foster and T. Craig. Pp. xx+1,874. (Association of Commonwealth Universities: Edinburgh, July 1970.) 195s; \$24.

THE *Commonwealth Universities Yearbook* remains one of the most tangible indices of the expansion of higher education, with 1,874 pages of text spread, this time, over three and not two columns. The editors explain that this change of format has been forced on them by the growth of the Commonwealth of the British Universities. If anything, the introductions to the various university systems are more complete than ever. There are exceptions; the Australian chapter, for example, skates round the question of salaries which seems continually to exercise Australian academics. The British chapter takes the view that the memorandum of guidance issued by the University Grants Committee in 1967 has enhanced the importance of the Committee of Vice-Chancellors, but has nothing to say about the row now brewing up between the universities and the British Government. If pages are anything to go by, Britain counts for roughly a third of the Commonwealth university system; India is one of the most quickly growing.

On the whole, the universities of the British Commonwealth seem to have been comparatively traditional in the design of their curricula, although the University of Toronto has broken new ground, or at least terminology, by bringing aerospace studies into academic life. American studies are booming, with thirty universities offering courses throughout the Commonwealth. Chinese studies are growing less quickly, with almost as many universities interested in Australia (six) as in Britain (nine). Molecular biophysics has made its appearance at Oxford, molecular sciences at several places (but the

year book declines to follow fashion by listing molecular biology separately from biology or genetics), while the number of brands of physics classified separately from physics pure and simple is thirty-four (including the no doubt fashionable physics of the Earth's environment at Oxford).

Future Galtons will find little to help them in the year book's collection of names. There are now, however, three Bernal's in academic life. Banerjee rates a column and a half in the index, while Bell claims only just over a column, the same rating as Bhattacharyya (the apparently less common variant with a single "y" brings the whole score up to nearly two columns). Predictably, Brown rates four columns (with and without an "e"). Chapman does well with nearly a column. Cook is less academically successful than Brown, Davis/Davies is less well represented than in the London telephone directory, even when both spellings are lumped together. One Galton persists, appropriately enough in London, and there are two Darwins and eight Huxleys.

JOHN MADDOX

Infamous Fungus

The Story of Ergot. By Frank James Bové. Pp. viii+297. (Karger: Basle and New York, 1970.) 66 Sw.francs; \$15.85; 66 DM; 132s.

It is now forty years since George Barger wrote his classical monograph *Ergot and Ergotism* in which he not only described in detail the poisonous role of rye ergot since mediaeval times, but also gave an account of the current knowledge of the biology of the ergot fungi and the chemistry and pharmacology of the ergot alkaloids. Since then, groups in many parts of the world have contributed extensively to research on the ergot alkaloids, notably in the fields of chemistry and pharmacology. Structural modification of the complex tetracyclic ergoline nucleus and its derivatives have led to novel and improved pharmacological properties which have reinforced the established place of these alkaloids in modern medicine. In more recent years, high yields of lysergic acid from deep fermentations have facilitated the semi-synthetic production of the medicinal alkaloids. Such progress has justified the several excellent specialized reviews which have appeared in the literature during the past ten years, notably Hofmann's splendid volume *Die Mutterkornalkaloide*.

Now Dr Bové has tackled the formidable task of writing a comprehensive monograph which, although conceived as a popular presentation, covers not only the pharmacognosy and pharmacology of ergot, but also ergoline biosynthesis. Bové has embraced a large and diffuse

bibliography and, consequently, presents a wealth of interesting information. Some references for 1968 are given, but the treatment of some of the more rapidly expanding topics is necessarily out of date. The author's lack of professional scientific involvement in ergot research, coupled with a marked tendency to over-dramatize, has resulted in some inadequate assessment of the literature and the perpetration of erroneous reports. For example, the publication which wrongly described 12-hydroxystearic acid (instead of ricinoleic acid) as a major component of rye ergot sclerotial oil is twice mentioned and given prominence as having reported a novel component.

The most striking feature of this book is the unfortunate style in which the subject matter is presented and which greatly detracts from its readability. This may be best illustrated by the following extract which opens the section on the chemistry of ergot: "The chemistry of ergot is complex. Compound complex. Compound because most alkaloids appear in pairs or triads. Most amino acids too. Perhaps the pigments also. Complex because the great number of substances in ergot are—within their groups—very similar. Thus difficult to separate. And isolate. And of course difficult to determine their true structure. Especially of the alkaloids. And pigments. This has now been done. Almost. But still several alkaloids remain to be discovered. Several non-alkaloidal substances too. Pigments. Enzymes. Glucans perhaps. The chemistry of ergot remains complex. And subtle too". It is a great pity that the considerable work involved in preparing the subject matter could not have been complemented by a presentation which, while thrilling to read, still had literary merit.

There is no doubt that the story of this most famous fungus could command a wide readership but this book is unlikely to achieve this goal. The subject is liberally endowed with intrinsic interest—poisoning shrouded in mediaeval folklore, herbal medicine, modern obstetrics and migraine therapy, complex pharmacology, industrial fermentations, plant pathology, chemistry and biochemistry, and the more recent abuse of the hallucinogenic drug LSD. If this book were to be re-written, while retaining its overall plan, it could become an attractive reference volume of lasting value.

P. G. MANTLE

Counsel about Cancer

What We Know About Cancer. Edited by R. J. C. Harris. Pp. 240+6 plates. (Allen and Unwin: London, November 1970.) 50s boards; 35s paper.

THE overwhelming need for a book which describes accurately what is known about

cancer in brief and simple terms is glaringly exposed in the last chapter of this book. Widespread ignorance of the excellent prognosis for many patients with cancer remains prevalent, not only among laymen, but also among medical students and nurses. It should be widely publicized that certain kinds of cancer can nowadays almost certainly be cured, and that, even in the more refractory forms of the disease, up to 75 per cent of the victims can be cured if an early diagnosis is made. The need to abolish stigma and fear, which are themselves responsible for hundreds of unnecessary deaths each year, is urgent.

Awareness of this need has prompted some officials and members of the British Cancer Council, all men of high international standing, to produce this book, presumably with the object of making the necessary information available to the public. I use presumably because, unfortunately, it is not immediately apparent what audience is being aimed at. Indeed, my chief criticism of this collection of essays is that I feel it has failed to get its audience into clear focus. On the cover it states "This book . . . is designed for the ordinary reader as much as for doctors and the medical world". I doubt that it is possible to write meaningfully on this subject for both. It is therefore probably suitable as general reading for nurses and for the informed and interested layman, but does not contain enough detail on most subjects for medical students. On the other hand, some of the chapters are, I suspect, too technical for the non-specialist.

Three chapters aim at about the right level. That by R. J. C. Harris (who edits the volume) on the history of cancer research provides a lucid and interesting summary of the field; it is marred only by a liberal spattering of complex chemical formulae which I would guess to be meaningless to most ordinary people. The account of the role of surgery in the management of cancer by Sir John Bruce has the down-to-earth, factual incisiveness one might expect of a surgeon. The most readable chapter of all is that on the social context of cancer by John Wakefield; intelligent, precise and thought-stimulating. Writing about lung cancer caused by cigarette smoking, for example, he points out that the total deaths in Britain every year are equivalent to the annihilation of every man, woman and child in Ilfracombe, Llangollen, Minehead and Penrith. "If it were some mystery virus that wiped out nearly 30,000 people each year, the public clamour for action by medical and governmental authorities would be instant and deafening." These are the sort of words that strike home hard.

There is a great deal of interest in the rest of the book, ranging from factual outlines of radiotherapy and chemotherapy, to accounts of the basic nature

and mechanism of cancer and some speculation on the control of the disease in the future. I hope many people will buy and read this book, because although it could have been done a little better, it is still likely to be one of the best books on cancer available to the general public. Moreover, the authors have donated their royalties to a worthy cause—the British Cancer Council—whose altruistic motives are outlined in the first chapter of the book.

JOHN PAUL

Sound and Hearing

Foundations of Modern Auditory Theory. Vol. 1. Edited by Jerry V. Tobias. Pp. xv+446. (Academic: New York and London, August 1970.) 210s.

THIS volume comprises eleven essays. Two of them deal with pitch analysis, three with masking and related phenomena, two with cochlear mechanics, two with auditory neural processing, one with lesions of auditory structures and one with musical perception. According to the editor's preface this varied collection is intended to cover areas not presently well reviewed and to provide a source book for readers "who know enough about hearing . . . to contribute a chapter themselves some day".

As a source book it leaves something to be desired, in that it fails in many cases to cover adequately the literature, particularly the more modern material. Indeed, in a footnote to the essay on cochlear processes, the author cites as his principal sources reviews written in 1962, 1960 and 1957, and this is an area where advance has been rapid in the past ten years. It might be argued that the foundations, even of modern auditory theory, should be historical, and this is certainly valid. Such foundations should not, however, recapitulate old interpretations which subsequent work has shown to be of doubtful validity or even downright wrong, as happens in several essays here. One does not, of course, expect a catalogue of every known reference in a work of this type, but an author should, hopefully, show familiarity with recent major developments in the field he is reviewing. At least one of the essays presents an extreme view of its topic—a deliberate policy, the editor claims—but one that again does not seem to be appropriate to the foundations of a subject.

The prospective reader would be less liable to disappointment if he were not led to expect that he would acquire a survey of the foundations of auditory theory; rather this is a collection of essays by well known workers on various subjects in the auditory field—some are well informed, others less so, some critical, some uncritical, some really filling a need,

others a rehash of material readily available elsewhere long ago. Among those that certainly deserve praise is the excellent essay by Scharf on critical bands; previously it was necessary to search through a very scattered literature for information about this subject.

I. C. WHITFIELD

Fruits of Progress

The Economic Prospects for Horticulture. Edited by E. D. Sargent and S. J. Rogers. (An Agricultural Adjustment Unit Symposium.) Pp. xiii+142. (Published for the Agricultural Adjustment Unit, University of Newcastle upon Tyne. Oliver and Boyd: Edinburgh, October 1970.) 30s.

COMMERCIAL horticulture (the intensive production of fruit, vegetable and flower crop plants) is in the midst of a revolution that started in the late 1940s and has been gathering momentum ever since. The chief result of this revolution has been increasing yield from a shrinking acreage, produced by a labour force that gets smaller each year. In spite of the increase in efficiency, there have been many pessimistic statements recently about the future prospects for horticulture, particularly in relation to the possible entry of the United Kingdom into the Common Market. On the other hand, there are many growers who are very optimistic about the future of the growing and commercial side of the industry and are increasing their capital investments in it.

This book gives a sound picture of the horticulture industry as it has developed recently in the United Kingdom, and as it has been influenced by Government policy at home and by changes in international trade. It is based on a series of ten papers presented at Wye College, London, in March 1969, and as there are thirteen authors, including the editors, it is not surprising that divergent views are expressed. There is no attempt to hide the many adverse features with which horticulturists have to grapple, and the economic pressures on the industry at present, from the producers, the processors, and the distributors of its products, are the subject of these papers. Less relevant to the title of the book, but a very interesting paper nevertheless, is that on the organization of research in horticulture in the United Kingdom. Like much in the management and marketing sides of the industry, research and extension need drastic overhaul. They are among the best of such services in the world, but if they are to help the grower to lead in horticultural production in Europe during the next thirty years considerable rethinking of aims and methods is needed. That all is not well with the ways in which commercial horticulture has been developing on the Continent

during recent years is clearly brought out, and UK growers should not overestimate their competitors or underestimate their own strengths and advantages.

The trend in horticulture, as in other businesses, is towards cooperation and amalgamation. The difficulties that the small-scale growers, distributors and retailers have been facing will intensify, and the inefficient will be forced to leave the industry. This trend is recognized by the universities, who are paying increasing attention to management techniques and economics, and not merely to horticultural science, in the education of future managers for the large production and distribution organizations. This aspect of the industry—the education of future leaders—is hardly dealt with in the book, yet it will profoundly influence the speed and direction of development. Horticulture is usually regarded as a synonym for the intensive production of agricultural crops, and it is interpreted so in this book. It must not be forgotten, however, that amenity horticulture will continue to be increasingly important in human affairs as the prosperity of the United Kingdom and Europe grows. In addition to producing ornamental plants, horticulturists will be closely concerned with the planning and maintenance of the environment, especially in urban areas.

It was not the intention of the editors to present a "blueprint for future policy-making", but to help horticulturists and the public to see where the industry stands today, and the direction in which it is likely to move tomorrow. They succeed, for the book is readable and is not overweighted with statistics and jargon. It can be recommended to all who are interested in food production in Britain and the well-being of one of the country's basic industries.

L. BROADBENT

The Simplest Reductant

The Hydrated Electron. By Edwin J. Hart and Michael Anbar. Pp. xiii + 267. (Wiley Interscience: New York and London, October 1970.) 125s.

ALTHOUGH solvated electrons in liquid ammonia and similar solvents had been recognized for many years, it was not until 1962 that conclusive evidence was obtained for the existence of the hydrated electron as a definite species with characteristic properties. It had been known for some time that irradiated aqueous solutions contained two different reducing species, sometimes described as different "kinds" of hydrogen atom, but the identification of one of these as a hydrated electron (e_{aq}^-) had to await the demonstration that it possessed a negative charge and a strong optical absorption spectrum which resembled that of the ammoniated electron, and F-centres in crystals. During the past eight years there has been intense

activity in following up this discovery, especially in studying the reactions of e_{aq}^- with inorganic and organic species. *The Hydrated Electron* quotes some 400 references which bear witness to this flood of new knowledge.

This field of research has a strange aspect to the student of conventional mechanisms and kinetics in solution. Typical concentrations of e_{aq}^- are 10^{-7} M, and its concentration can be measured down to 10^{-9} M, so that trace impurities are often of great importance. Sixteen different reactions are required to account for the disappearance of e_{aq}^- in pure water, and because of its transient nature, any reaction with a solute species having a second-order velocity constant less than 10^6 l. mol $^{-1}$ s $^{-1}$ is termed "slow", and may be difficult to detect. A combination of pulse radiolysis and competition methods has made it possible to measure the rate constants of some 400 reactions, many of them of the order of 10^{10} l. mol $^{-1}$ s $^{-1}$, and techniques have been developed to study transient species in periods as short as 2×10^{-11} seconds. Because e_{aq}^- is the simplest reducing agent, its reactions are of great interest, and considerable progress has been made in understanding the large amount of experimental information now available.

Dr Hart and Dr Anbar have made important contributions to the study of the subject and their book gives a comprehensive account of our present knowledge of the hydrated electron, including its physical properties and its reactions in inorganic, organic and biological systems. It concludes with a chapter on experimental techniques and a number of useful numerical tables. Although the preface speaks of the importance of the subject in general chemical education, the amount of detail provided is certainly too great for the non-specialist student, and the book is more suitable for those intending to enter research in this field. There are some signs of hasty preparation or proof reading: for example, "electron affinity", "cabonylic", "vandate", "triagonal", "assymmetry", "concieve", "propionit-riple", "developes" and "nitrozobenzene". In general, however, the exposition is clear and is supplemented by excellent diagrams and chapter summaries.

R. P. BELL

Material Images

Modern Diffraction and Imaging Techniques in Material Science. Edited by S. Amelinckx, R. Gevers, G. Remaut and J. Van Landuyt. Pp. viii + 745. (North-Holland: Amsterdam and London, 1970.) 252s.

FOR many years now, summer schools dealing with various branches of physics have been held in Europe. In 1969, the first session devoted to materials science

was held at Antwerp and dealt with diffraction and imaging techniques. The lectures from this conference have now been collected and published. The topics covered include transmission, scanning and mirror electron microscopy, low and high energy electron diffraction, X-ray and neutron diffraction, X-ray topology and field ion microscopy. In each case, the theory of diffraction or imaging, the experimental techniques, and the various applications are described in a particularly coherent way. The list of contributors includes many of the most eminent names in modern diffraction.

At the outset it needs to be said that there are two ways in which materials scientists use these modern techniques. The first is in an observational way, analogous to the way in which an optical microscope is used. In many cases what one is seeing is obvious, so that with only a limited knowledge, transmission and scanning electron microscopy or X-ray topology can be used quite successfully. The second way of using these diffractive and imaging techniques goes far beyond the simple observational approach. It involves using the techniques in a most sophisticated manner, applying diffraction theory to interpret what are often very complicated images and patterns. That is what this book is about.

The book starts with a treatment of the kinematical and dynamical theory of electron diffraction, and the application of dynamical theory to line defects in order to calculate intensity profiles. This approach is then extended by a chapter dealing with the use of computer simulation techniques to produce "dot" pictures, like newsprint, which can be directly compared with the images seen in the electron microscope. Among other topics, there is a fascinating discussion of Kikuchi lines in transmission electron microscopy which demonstrates the power of the electron microscope for accurate diffraction studies. In scanning electron microscopy, which rightly takes up a good part of this book, the analogue to Kikuchi lines is the electron channelling patterns, which are extremely important, for they represent the one way of observing crystallographic effects. The problems, and the experimental conditions for obtaining them, are clearly described.

Although many of the topics in this book are treated in a general way, several pieces of information are included which cannot readily be found in the literature, and which should prove most valuable to the researcher working on his own. This poses an interesting question. Who outside of the prominent research groups will utilize in an advanced way these powerful techniques? Certainly not the average materials scientist. Nevertheless, this book may prove of value to the adventurous researcher working in isolation.

E. LILLEY

CORRESPONDENCE

In Vivo Difficulties

SIR,—The use of the terms “in vitro” and “in vivo” is now deeply entrenched in the scientific literature. They are used to denote the difference between experiments performed outside the living organism (although often with living tissue, and those carried out inside the organism. The use of the two terms, although hallowed by time, sometimes causes difficulty, especially as editors of learned journals differ in the extent of their tolerance and degree of their pedanticism. Some editors are prepared to accept the terms virtually as the author proposes, irrespective of syntactical or scientific niceties. Some turn a blind eye to their suspiciously foreign sound and are prepared to admit them as current English usage. Others, more severe, by clapping the terms in italics, clearly still regard them as aliens against whom the innocent reader must be warned. Hyphens between the two parts of each term are not usually required, but on occasions have been insisted upon by the illiberal of outlook. Although strictly “in vitro” and “in vivo” are adverbial phrases (and are only so used by cognoscenti) they are now often misused as adjectives. Hence one reads of “in vitro experiments” and the even more disgraceful “in vitro results”. Even “semi-in-vivo” (hyphenated surely) experiments have recently been threatened. Fowler, unfortunately, wrote before such indignities became common, and has nothing to say on the matter.

With due awareness of Lord Chesterfield's famous maxim, I should like to suggest the introduction of two new words to replace “in vitro” and “in vivo”. These would be the simple adjectives “vital” and “vival” respectively. The new words are short, their derivation is etymologically pure and their meaning by past association) is clear, when referring either to the tests themselves or to the results of tests. Moreover, they will never need italics or hyphens. Reference to various technical dictionaries has disclosed, perhaps surprisingly, no prior use of such adjectives. Although their introduction, it is realized, would not be so traumatic as the introduction of SI units, nor so subversive as the substitution of “retinol” for vitamin A', there are bound to be views in favour of the status quo and it would be interesting to hear them.

Yours faithfully,

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Billion Confusion

SIR,—Teodor Juskiewicz (*Nature*, 228, 297; 1970) referred to the American practice of using the word “billion” to mean 10^9 instead of 10^{12} and he appealed to American colleagues not to use the misleading term parts per billion.

I support Juskiewicz's appeal and suggest that it is time that some agreement was reached to avoid misunderstandings, which can arise by the use of this, at present, equivocal word.

To my mind the word “billion” means a million to the power of two, similarly “trillion” means a million to the power of three and so on using suitable prefixes added to the root “-illion” for numbers of the type 10^{6n} (where n is an integer).

There is some need for a simple name for the number 10^9 which would be preferable to the rather clumsy “thousand million”. The word “milliard”, obviously familiar to Juskiewicz and, I understand, currently used in France, seems an obvious choice. Furthermore, this word could form the basis of a system of naming large numbers of the type $10^{(6n+3)}$ in the same way that “million” has for the 10^{6n} numbers. Thus 10^{15} would be called ailliard and 10^{21} a trilliard, and so on.

Yours faithfully,

R. M. BOROUGHS

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Molecular Mass

SIR,—Dr Edsall has explained (*Nature*, 228, 888; 1970) the useful distinctions that should be preserved among the expressions, molecular mass, relative molecular mass (commonly called “molecular weight”) and molar mass. These quantities have respective dimensions: mass, unity (“dimensionless”) and mass $\times$ (amount of substance) $^{-1}$. The common unit of molar mass (not its dimension) is the gram per mole (symbol, g/mol or g mol $^{-1}$). Among recognized units of molecular mass is the unified atomic mass unit (symbol u), defined as the fraction $1/12$ of the mass of an atom of the nuclide ^{12}C ($1\text{ u} = 1.660\,53 \times 10^{-27}$ kg approximately), and for which Dr Edsall recommends the simpler name, dalton, widely used by biochemists. (His examples of different statements expressing the same fundamental facts should have read:

“the molar mass of protein X is 25,000 g mol $^{-1}$ ”, “the molecular mass of protein X is 25,000 daltons”, and “the relative molecular mass (that is, molecular weight) of protein X is 25,000”.)

The 14th General Conference of Weights and Measures (CGPM) of the International Bureau of Weights and Measures, convening in 1971, will consider a recommendation approved in 1969 by the International Committee on Weights and Measures (CIPM) to include the mole as a base unit of the International System of Units (SI), besides the six base units on which the system was established in 1960 (the metre, the kilogram, the second, the ampere, the kelvin, and the candela). The additional base unit is needed to introduce SI units for the “molar” physical quantities (molar volume, molar mass, molar heat capacities, molar enthalpy of formation, etc.). The appropriate physical quantity corresponding to the concept that different substances have natural molecular constitutions (the word “molecular” here being used in a broad sense to include any specified constituent entities, whether they be molecules, atoms, ions, ion pairs, or other aggregates) has not until recently been identified by a commonly recognized name. The name, “amount of substance”, has now been adopted by the International Union of Pure and Applied Chemistry, the International Union of Pure and Applied Physics, and the International Organization for Standardization to define a physical quantity proportional to the number of constituent entities of that substance (molecules or other entities, such as may be specified by a chemical formula). The proportionality factor is the same for all substances and may be taken to be the reciprocal of the Avogadro constant. A unit for the physical quantity, the mole, has long been recognized. The definition given by the CIPM in 1967, confirmed in 1969, and included in the draft proposal prepared for the 14th CGPM introducing the mole as a base unit in the SI, is as follows¹:

The mol is the amount of substance of a system which contains as many elementary entities as there are atoms in 0.012 kilogram of carbon 12.

Note: When the mol is used, the elementary entities must be specified and may be atoms, molecules, ions, electrons, other particles, or specified groups of such particles.

If the 14th CGPM accepts the mole so defined as an SI base unit, then the SI unit of molar mass will be the kilogram per mole (kg mol $^{-1}$). This unit is large for ordinary chemical purposes and the common unit, gram per mole (1 g mol $^{-1}$

$= 10^{-3} \text{ kg mol}^{-1}$), will continue in use as an accepted decimal sub-multiple of the SI unit. However, the SI unit itself is suitable for expressing values of the molar mass for macromolecular substances. Thus, one could add to Dr Edsall's equivalent statements the alternative: "the molar mass of protein X is 25 kg mol $^{-1}$ ".

Although the unit of mass, "unified atomic mass unit", is outside the SI, it has been recognized by the CIPM as useful in specialized fields of scientific research¹. Its value expressed in the SI unit, the kilogram, is derived by experiment and is therefore not known exactly. Although in general one should be chary of proliferating special names, the present name for this unit, even when contracted to "atomic mass unit" (the term "unified" distinguishing it from slightly different earlier units based on ^{16}O and on $\text{O} = 16$), is not notably convenient or informative. Dr Edsall's suggestion that it be renamed the dalton merits consideration by the international agencies concerned with standardization of chemical and physical nomenclature so long as the unit itself continues to be recognized by the CIPM as one of those useful outside the SI in specialized fields. It would not be helpful if scientists in different fields employed different names for the same unit.

Yours faithfully,

MARTIN A. PAUL

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¹ *The International System of Units (SI)*, translation approved by the International Bureau of Weights and Measures of its publication, *Le Système International d'Unités*, prepared jointly and published independently by the National Physical Laboratory, UK, and the National Bureau of Standards, USA: National Bureau of Standards Special Publication 330, 1970, US Government Printing Office, Washington, DC 20402.

Definition of Intelligence

SIR,—Because others (*Nature*, 228, 1008; 1970) have commented on the definition of intelligence put forward by Fatmi and Young (*Nature*, 228, 97; 1970) and subsequently extended by myself (*Nature*, 228, 589; 1970), I would like to make some further observations.

With regard to the letter from P. M. Muller, the process of induction would be covered by my own definition, as would "synthetic a priori". However, processes of reasoning from the part to the whole, from the particular to the general, and from the individual to the universal, are not identical and isomorphic processes, nor are they symmetrical with respect to deduction and induction.

If we accept Gödel's theorem, a single, finite automaton with a phrase-structure grammar can be either complete and consistent (closed) or universal (open). A Gödel complete system will accept only tautologies or empirically verifiable sense-data that have been specified in the instruction set, rejecting all other inputs as illogicality or "noise". The possibility of new or unspecified states is excluded. If we assume that human intelligence not only construes syllogisms, but also discovers, elucidates and initiates the previously unknown, then it is clear that this cannot be a property of Gödel complete automata (existing computers). Indeed, it would seem that an incomplete instruction set (a quasi-non-deterministic system) is a necessary condition for the emergence and evolution of intelligence, as we observe it in living systems. However, the possibilities of machines do not end with single finite-state machines or with phrase-structure grammars.

In my own work I have been considering the possibilities of hierarchical networks of automata, some of them backward deterministic¹, in an attempt to solve the Gödel theorem problem for quasi-non-deterministic systems, including brain-models. The basic idea is to

axiomatize the levels of the system independently and use negative feedback to control the universality (requisite variety) of both individual levels and the system as a whole. An essential part of the control system is an order: disorder detector, as suggested by H. B. Barlow in his letter. This type of system would also imply that the original definition of Fatmi and Young would be too broad to draw a valid distinction between men and machines.

With regard to the letter from H. A. Cook. Any system is quantifiable if one knows what to measure and how to measure it. It is another matter to decide whether such a quantification provides an adequate description of the system as a whole. The information-theoretic brain model mentioned above implies a physiological symbol-processing mechanism in the brain, which could form a substrate for the heritable components of both intelligence and linguistic behaviour. Since such a component would be determined by input-rate and digit-span, and would be invariant with respect to learning, it should be possible to isolate and quantify it given a calibrated digital input and criteria for assessing the output response in quantitative terms. With regard to a quantified definition of intelligence, without recourse to linguistic behaviour, we may be up against a special case of Richard's paradox.

The correspondence following Fatmi and Young's original letter has emphasized the need for further dialogue concerning the theoretical and philosophical aspects of machine and human intelligence, and it is gratifying to learn that the Cambridge Branch of the Brain Research Association is setting up a forum in this area of study.

Yours faithfully,

GORDON HYDE

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¹ Wang How, *A Survey of Mathematical Logic*, 175 (North-Holland, 1964).

Obituary

Dr J. E. Falk

JOHN EDWIN FALK, chief of the division of plant industry, Commonwealth Scientific and Industrial Research Organization, Canberra, died on October 25, 1970. Born in 1917 at Cessnock, NSW, he studied pharmacy at the University of Sydney, but finding that his interests lay in chemistry he completed a Bachelor of Science degree in 1942. After graduating he joined Professor V. M. Trikojus in an investigation of synthetic methods of preparation of essential drugs unavailable in war time Australia. In 1944 he became Chief Chemist at Bayer's in Sydney and at the

end of the war returned to research in the university on a Wellcome fellowship under Professor Adrian Albert. During this period his research into the mode of action of certain antimalarial drugs awakened his interest in biochemistry and led him into the field of haem pigments. In 1947 he was awarded a grant by the National Health and Medical Research Council to work at the Royal North Shore Hospital, Sydney, under Professor M. R. Lemberg, FRS. Here he investigated the prosthetic group of cytochrome oxidase and learnt a great deal about porphyrins.

In 1948, Falk was granted a Nuffield travelling fellowship and with financial

assistance from the National Health and Medical Research Council he went to University College Hospital Medical School in London to work with Professor C. Rimington, FRS. His research included a systematic study of the infrared spectra of porphyrins and haems as well as further work on cytochrome oxidase. He received his PhD in 1951. A "Nuffield Unit of Pyrrole Pigment Research" was established in Professor Rimington's department and Falk was appointed director. In 1953, he was awarded a Foulerton research fellowship by the Royal Society. During this period, he developed analytical methods for porphyrins and turned his attention

to the biosynthesis of porphyrins and haems.

His contact with Professor R. S. (now Sir Ronald) Nyholm, FRS, of the Department of Chemistry, University College, led to his interest in the coordination chemistry of porphyrins and metalloporphyrins. Much of his later research was concerned with an attempt to understand the spectral and biological properties of haemoproteins in terms of their coordination and physical chemistry.

In 1955 he returned to Australia and joined CSIRO as head of the biochemistry section of the Division of Plant

Industry. He was elected a Fellow of the Australian Academy of Science in 1961 and was president of the Australian Biochemical Society from 1964-66. In 1963 he succeeded Sir Otto Frankel, FRS, as chief of the largest division of CSIRO, and one of the major agricultural research institutions in the world. He devoted much effort to building bridges between the research of his division and the worlds of the farmer, the economist and the extension worker while maintaining the scientific excellence of the institution. He played an active part in discussions on defining a govern-

ment science policy and in developments in the social role of science.

Falk retained his own research interests and his book *Porphyrins and Metalloporphyrins*, published in 1964, reflects in the clarity and conciseness of its presentation his ability as a writer. He was an excellent flautist and played for many orchestras including the Sydney Symphony Orchestra; he did much to encourage musical activities in Canberra. A distinguished scientist and outstanding organizer, John Falk was also a warm hearted and generous friend. He will be sadly missed.

Announcements

New Year Honours

The following honours awards were announced on January 1: **Knight Bachelor**, Professor F. S. Dainton, for services to science and higher education; Dr G. E. R. Deacon, director of the National Institute of Oceanography; Wylie McKissock, neurological surgeon; **CBE**, Professor F. K. Bannister, University of Birmingham; Eric S. Booth, Central Electricity Generating Board; Professor J. G. D. Clark, University of Cambridge; Professor A. I. Darling, University of Bristol; Professor J. L. Gowans, for services to medical science; C. Joliffe, Science Research Council; W. Marsh, Rolls-Royce, Derby; Professor J. Walker, University of Dundee; D. J. Watson, Rothamsted Experimental Station; Professor A. Wilson, University of Liverpool; **OBE**, R. J. Adle, British Antarctic Survey; G. S. Innes, St Bartholomew's Hospital, London; E. I. Lloyd, Ministry of Aviation Supply; Professor A. L. Roberts, University of Leeds; J. S. M. Robertson, Western Regional Hospital Board (Scotland); S. J. Robinson, Mullard Research Laboratories, Redhill.

University News

Dr Arthur F. Turner, head of the optical Physics Department, Vacuum Coating Division, Bausch and Lomb Inc., has been appointed professor of optical sciences in the University of Arizona.

Dr R. H. Ottewill has been appointed to the chair of colloid science in the School of Chemistry, University of Bristol.

Dr Sven Paulin has been appointed professor of radiology at Harvard University and radiologist-in-chief at the Beth Israel Hospital, Boston.

Professor P. T. Matthews has been appointed head of the Department of Physics, Imperial College, University of

London, in succession to **Professor C. C. Butler**, on whom the title of professor of physics has been conferred. The title of professor of chemistry has been conferred on **Dr Mary R. Truter** in respect of her post at University College, London.

Mr Aron Holzel has been appointed to an additional chair of child health in the University of Manchester.

Dr William Anderson has been appointed to the chair of pharmaceutical technology in the University of Strathclyde.

Appointments

Mr George W. Cherry has been appointed director of the Aeronautical Operating Systems Division in the Office of Advanced Research and Technology, NASA.

Dr Byron Riegel, director of chemical research at G. D. Searle and Company, has been elected 1971 chairman of the board of directors of the **American Chemical Society** in succession to **Dr Milton Harris**.

Professor A. L. Hodgkin, president of the Royal Society, and **Professor P. B. Hirsch**, professor of metallurgy in the University of Oxford, have been appointed members of the **Council for Scientific Policy**, in place of **Lord Blackett** and **Dr C. E. Lucas**.

Miscellaneous

Mr Charles P. Ginsburg, vice president (advanced development) for the Ampex Corporation and **Professor Erwin W. Mueller**, Pennsylvania State University, have each been awarded a **John Scott medal** and a cash award of \$2,000 for their work in videotape recording and field-ion microscopy respectively.

The 1970 **MacRobert award** for engineering and technology has been presented to **H. R. Warman**, A.N. Thomas and **Dr P. E. Kent**, geologists with British Petroleum, for their geological and geophysical survey work in Alaska which

led to the discovery of the North Slope oilfields.

Nominations for the 1972 **Roussel prize** for outstanding work in the field of steroids are invited. The prize is worth \$6,000 and candidates may be of any nationality. Further information can be obtained from the secretary of the award committee, Professor J. Mathieu, Centre de Recherches, Roussel-Uclaf, 93 Romainville, France.

Applications are invited for the **Perkin centenary scholarships** and **Perkin travel grants**. The scholarships are intended to enable employees of industrial firms concerned with the manufacture or application of colouring materials to study at a university or technical college. The travel grants are available for teachers concerned with any aspect of the manufacture or applications of colouring matters to visit to gain experience in institutions other than their own. Further information and forms of application can be obtained from the secretary of the Perkin Centenary Trust, c/o The Chemical Society, Burlington House, London W1.

The **New York Cancer Research Institute** has established a number of fellowships for the support of qualified individuals who wish to receive training and experience in experimental or clinical cancer immunology. Applicants may be of any nationality and should hold an MD or PhD degree. The value of each fellowship will vary according to the experience and responsibility of the applicant. Further information can be obtained from Mrs W. B. Nauts, executive director, New York Cancer Research Institute Inc., 1225 Park Avenue, New York, NY 10028, USA.

ERRATUM. In the review "Derivatives of NH" by P. Sykes (*Nature*, 228, 1233; 1970), the first sentence in the second paragraph should read "There has in the past been some confusion over the naming of nitrenes, but the use of the definition in the first paragraph . . .".

British Diary

Monday, January 11

A Psychologist Looks at Induction (5.30 p.m.) Dr N. Wetherick, British Society for the Philosophy of Science, in the Joint Staff Common Room, University College London, Gower Street, London WC1.

Design and Maintenance of Basic Oxygen Steel Plant at Port Talbot (7.30 p.m.) Mr H. P. Boyce, Lincolnshire Iron and Steel Institute, jointly with the Iron and Steel Engineers Group and the Lincolnshire Panel of the Institution of Mechanical Engineers, at North Lindsey Technical College, Kingsway, Scunthorpe.

Invention as Part of Education (6.30 p.m.) Professor M. W. Thring, Institution of Electrical Engineers, at the University of Newcastle upon Tyne.

Metrication (6 p.m.) Mr E. P. Tomblin, Institution of Electrical Engineers, at UWIST, Cardiff.

Tuesday, January 12

A Review of Computer Control (6 p.m.) Mr S. L. H. Clarke, Institution of Electronic and Radio Engineers, at 9 Bedford Square, London WC1.

Current Trends in Radioastronomy (7.30 p.m.) Mr M. J. S. Quigley, Institution of Electrical Engineers, at the PO College, Horwood House, Bletchley, Bucks.

Disc Brake Pad Wear Evaluation (6 p.m.) Mr M. W. Moore and Mr B. Walton, Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

Electronics in Archaeology (6.30 p.m.) Mr E. T. Hall, Institution of Electrical Engineers, jointly with Farnborough District Archaeological Society, at Farnborough Technical College, Farnborough, Hampshire.

Hangar 01 at Heathrow Airport for the Boeing 747 Aircraft (5.30 p.m.) Mr K. J. Joyner, Professor Z. S. Makowski and Mr R. G. Taylor, Institution of Civil Engineers, at Great George Street, London SW1.

Hybrid Computers (6.30 p.m.) Mr J. Nelson, Institution of Electrical Engineers, at the University of Leeds.

Metallurgy in Space (6.15 p.m.) Mr G. Llewelyn, Tyne Wear Metallurgical Society, at the University, Newcastle upon Tyne.

Numerical Control of Machine Tools (6 p.m.) Mr D. F. Walker, Institution of Electrical Engineers, at the Carlton Hotel, Edinburgh.

Statistical Evaluation of Cold Starting Systems in Automobiles (7.30 p.m.) Mr T. Ince, Society of Environmental Engineers, at the University of Birmingham.

The Impact of Communications on Society (6.15 p.m.) Professor E. C. Cherry, Institution of Electrical Engineers, at UMIST, Manchester.

Two Pack Epoxy Coatings (7.30 p.m.) Mr A. McKay, Oil and Colour Chemists' Association, at the Griffin Hotel, Boar Lane, Leeds.

Wednesday, January 13

Data Transmission Over Radio Links (6.30 p.m.) Mr J. D. H. Alexander and Mr J. S. Reynolds, Institution of Electrical Engineers, jointly with IERE, at the University of Southampton.

Electronics and the Economy (6.30 p.m.) Mr I. Maddock, Institution of Electrical Engineers, at King Edward VI Grammar School, Chelmsford, Essex.

Integrated Circuits for Colour Television (6 p.m.) Mr J. C. MacKellar, Institution of Electronic and Radio Engineers, at 9 Bedford Square, London WC1.

The Application of Linear Induction Motors to High Speed Transport (7.30 p.m.) Professor F. T. Barwell, Institution of Electrical Engineers, at Torella Restaurant, Preston.

The Dynamic Transfer Characteristics of Reciprocating Engines (6 p.m.) Mr D. E. Bowns, Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

The Reduction of Aircraft Noise (two-day conference) Institute of Physics and the Physical Society jointly with the Royal Aeronautical Society, at Filton, near Bristol.

The S.S. 'Great Britain' and Its Salvaging Mr Richard Goold-Adams, Royal Society of Arts, at John Adam Street, London WC2.

The Use of Carbon Black in Paints, Plastics and Printing Inks (4.30 p.m.) Mr B. E. Thomas, Oil and Colour Chemists' Association, at the Manchester Literary and Philosophical Society, 36 George Street, Manchester 1 (Student Lecture).

Thursday, January 14

Building in the Tropics (5.50 p.m.) Mr W. Kinnburgh, Society of Chemical Industry, at 14 Belgrave Square, London SW1.

Is Combustion Theory Applicable? (6 p.m. discussion) Institution of Mechanical Engineers, at 1 Birdcage Walk, London SW1.

MOS Transistors and Microelectronics (7 p.m.) Mr M. B. Bandali, Institution of Electrical Engineers, at the University, Edgbaston, Birmingham.

The History of Control Science (6.15 p.m.) Professor H. A. Prime, Institution of Electrical Engineers, at University College of Swansea, Singleton Park, Swansea.

Utilization Research in the Electricity Supply Industry (7 p.m.) Mr G. Ratcliff, Institution of Electrical Engineers, at the University of Dundee.

Friday, January 15

Analytical Aspects of Food (7 p.m.) Mr K. Durham, Society for Analytical Chemistry, at Bristol Polytechnic, Ashley Down, Bristol.

Electro-Organic Syntheses (6.30 p.m.) Dr J. H. P. Utley, Society of Chemical Industry, at 14 Belgrave Square, London SW1.

Saturday, January 16

A Winter in Mongolia (3.30 p.m.) Mr Stephen Jenkins, Inner London Education Authority, at the Horniman Museum, London Road, Forest Hill, London SE23.

Reports and Publications

not included in the monthly Books Supplement

Great Britain and Ireland

Greater London Council. Annual Report of the Scientific Adviser for 1969. Pp. 96. (London: GLC, Scientific Branch, 1970.) [2311]

University Grants Committee. First Employment of University Graduates, 1968/1969. Pp. 50. (London: HMSO, 1970.) 13s (65p) net [2311]

Department of Education and Science. Design Note No. 5: The School and the Community. Pp. 40. (London: Architects and Building Branch, Department of Education and Science, Curzon Street, 1970.) [2311]

University of Nottingham, Report of the School of Agriculture, 1969/1970. Pp. 149. (Sutton Bonington, Loughborough: University of Nottingham School of Agriculture, 1970.) 10s. [2311]

International Planned Parenthood Federation. Working Paper No. 5: The Relationship Between Family Size and Maternal and Child Health. Pp. 27. (London: International Planned Parenthood Federation, 1970.) [2311]

Radiation Protection. ICRP Publication No. 16: Protection of the Patient in X-ray Diagnosis. A Report by a Task Group of Committee 3 of the International Commission on Radiological Protection. Pp. 46. (Oxford and New York: Pergamon Press, 1970. Published for ICRP.) 25s; \$3.40. [2311]

Oundle School Natural History Society. Annual Report for 1969. Pp. 42. (Oundle, Peterborough: Oundle School Natural History Society, 1970.) [2311]

Why Britain Needs Conservation Policy for the Environment. Pp. 15. The Worlds' Too Small. Presidential Address to The Conservation Society by the Rt. Hon. Sir David Renton, MP. Pp. 10. The Population Problem. (Correspondence between the Prime Minister, the Rt. Hon. Harold Wilson, MP and the Rt. Hon. Sir David Renton, MP. Pp. 13. (London: Conservation Society, c/o Mrs L. Hettner, 30 Westbourne Park Villas, W2, 1970.) [2511]

Chatham House: PEP. European Series No. 15: Regional Policy in Britain and the Six—The Problems of Development Areas. By Harold Lind. Community Regional Policy. By Christopher Flockton. Pp. 76. (London: Chatham House and PEP, 1970.) 13s. [2411]

Ministry of Transport: Road Research Laboratory. RRL Report LR 363: Air-Entrained Concretes—a Survey of Factors Affecting Air Content and a Study of Concrete Workability. By D. F. Cornelius. Pp. 18 + 4 plates. (Crowthorne, Berkshire: Road Research Laboratory, 1970.) *gratis*. [2511]

The Anti-Locust Research Centre—a Concise History to 1970. By Jeremy Roffey. Pp. 36. (London: Anti-Locust Research Centre, Ministry of Overseas Development, 1970.) [2511]

The Pre-Grinding Preparation of Diamond Abrasive Grinding Wheels. (Diamond Information L24). Pp. 6. (London: De Beers Industrial Diamond Division, 7 Rolls Buildings, Fetter Lane, 1970.) *gratis*. [2511]

Department of Education and Science. Statistics of Education 1969. Vol. 5: Finance and Awards. Pp. xv + 59. (London: HMSO, 1970.) 26s. [2611]

National Reference Library of Science and Invention. A Guide to Referativnyi Zhurnal. By E. J. Copley. (Occasional Publications.) Pp. 28. (London: National Reference Library of Science and Invention, 1970.) [2611]

The Interpretation and Development of Quantum Theory. By G. N. Fowler. (Inaugural Lecture delivered in the University of Exeter on 25 November 1969.) Pp. 27. (Exeter: The University, 1970.) 5s. [2611]

The Radiochemical Centre, Amersham Radiopharmaceuticals and Clinical Radiation Sources 1971. Pp. 103. Radiochemicals 1971. Pp. 95. Radioactivity Standards 1971. Pp. 31. (Amersham: The Radiochemical Centre, 1970.) [2611]

Medical Research Council. Biochemical Research in Psychiatry: Survey and Proposals. Report by a Council Committee. Pp. iv + 35. (London: HMSO, 1970.) 6s (30p) net. [2711]

Philosophical Transactions of the Royal Society of London. A: Mathematical and Physical Sciences. Vol. 268, No. 1187, (19 November 1970): Lunar and Solar Magnetic Variations at Abinger—Their Detection and Estimation by Spectral Analysis via Fourier Transforms. By D. I. Black. Pp. 233–263. 17s; \$2.20. Vol. 268, No. 1188 (19 November 1970) Theory of the Current-Voltage Characteristics of SNS Junctions and other Superconducting Weak Links. By J. R. Waldram, A. B. Pippard and J. Clarke. Pp. 265–287 12s; \$1.55 (London: The Royal Society, 1970.) [2711]

The Arblaster Case (The findings of a Commission of Inquiry established by the Council for Academic Freedom and Democracy in October 1970.) Pp. 16. (London: Council for Academic Freedom and Democracy, 1970.) 3s (15p.) [2711]

Wood Bending Handbook. By W. C. Stevens and N. Turner. Pp. 110 (26 plates). (Forest Products Research Laboratory.) (London: HMSO, 1970.) 35s. [2711]

Other Countries

Twelfth Activity Report of the European Nuclear Energy Agency. Pp. 116. (Paris: OECD, European Nuclear Energy Agency, 1970.) [2311]

Journal of Physical Oceanography, Vol. 1, No. 1, January 1971. Pp. 1–62. Published quarterly. Subscription: \$20 per year to non-members of the Society; \$10 per year to members of the Society. Subscriptions outside the US carry an additional charge of \$2 per year for postage. Single issues \$6 non-members; \$3 members. (Boston, Mass.: American Meteorological Society, 1971.) [2411]

Regional Congress of the International Union of Physiological Sciences, organized by The Academy of the Socialist Republic of Romania; The Academy of Medical Sciences; The "D. Danielopolu" Institute of Normal and Pathological Physiology; and the Romanian Society of Physiology. Abstracts of Papers: Invited Lectures; Advances in Physiological Sciences; Symposia; Free Communications and Discussion Groups, Brasov, Romania, August 10–16, 1970. Pp. 582. (Bucharest: The Academy of the Socialist Republic of Romania, 1970.) [2511]

Records of the Australian Museum, Vol. 28, No. 3, (29 September 1970): The Genus *Chlorinoides* (Crustacea, Brachyura, Majidae). 2. *Chlorinoides goldsboroughi* Rathbun from Eastern Australia, *C. tenuirostris* Haswell and a New Species from Western Australia. By D. J. G. Griffin. Pp. 65–76. (Sydney: The Australian Museum, 1970.) \$0.50

Smithsonian Contributions to Zoology, No. 59: Exotic Fishes and Other Aquatic Organisms Introduced into North America. By Ernest A. Lachner, C. Richard Robins, and Walter R. Courtenay, Jr. Pp. 29. (Washington, DC: Smithsonian Institution Press, 1970. For sale by US Government Printing Office.) \$0.45. [2511]

Forest Research in India, 1958/59. Part 2: Reports from Indian States. Pp. 95. Rs. 6.75; 15s 9d; \$2.43. Forest Research in India, 1959/60. Part 2: Reports from Indian States. Pp. 88. Rs. 6; 14s; \$2.16. Forest Research in India, 1960/61. Part 2: Reports from Indian States. Pp. 143. Rs. 9.75; 22s 9d; \$3.51. Indian Forest Bulletin No. 260, (New Series.)—Wood Seasoning. Preliminary Experiments on the Dimensional Stabilization of Some Indian Hardwoods with Polyethylene Glycol—1000. By S. N. Sharam and R. N. Madan. Pp. 6. Rs. 1.55; 3s 8d; \$0.65. Indian Forest Leaflet No. 190: FRI Portable Charcoal Kiln. By S. Ramaswami. Pp. 5 + 2 plates. Rs. 0.75; 1s 9d; \$0.27. (Delhi: Manager of Publications, 1970.) [2611]

World Health Organization. Technical Report Series, No. 454: Multipurpose Serological Surveys and WHO Serum Reference Banks—Report of a WHO Scientific Group. Pp. 95. (Geneva: WHO; London: HMSO, 1970.) 5 Sw. francs; 10s; \$1.75. [2711]

Australian Academy of Science. Year Book, June 1970. Pp. 124. (Canberra City: Australian Academy of Science, 1970.) [2711]

US National Ocean Survey. Bathymetric Map. Chesapeake Bay—Potomac River Entrance—Plate 8. Bathymetry at 2-Meter Intervals, Referenced from Mean Low Water. Universal Transverse Mercator Projection. Datum: N.A. 1927. (Washington, DC: National Ocean Survey, 4200 Connecticut Ave., N.W., 1970.) [2711]

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